

Washington State Newborn Screening Health Care Provider Manual

What should I know about the information provided on this page?

This information is intended to explain the necessary collaboration between the Washington State [Newborn Screening Program](#), health care facilities (hospitals, local health departments, clinics), health care providers (pediatricians, family practice physicians, nurse practitioners, midwives), and families of newborns to help make newborn screening successful. Included is information about the disorders detected by the program and answers to frequently asked questions about newborn screening, such as the availability of expanded screening, the effects of transfusions, and the storage of newborn screening cards. We hope that you will find this information helpful. If you have any questions about information contained within this manual, please contact us at 206-418-5410, 1-866-660-9050 (toll-free) or NBS.Prog@doh.wa.gov. The Newborn Screening program encourages all parents to discuss any concerns they have regarding newborn screening results with their health care provider or with follow-up staff at the Newborn Screening program.

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Introduction

Newborn screening is a population-based, preventive public health program that is carried out in every state in the United States and in many countries throughout the world. It enables early identification of selected disorders that, without detection and treatment, can lead to permanent mental and physical damage or death in affected children. The goal of newborn screening is to facilitate prevention of developmental impairments (such as mental retardation and neurological deficits), delayed physical growth, severe illness, and death through early detection and intervention.

Across the United States, there are variations in the disorders for which each state screens. Infants born in Washington State are currently screened for phenylketonuria (PKU), congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH), galactosemia, biotinidase deficiency, homocystinuria, maple syrup urine disease (MSUD), medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, cystic fibrosis (CF), and sickle cell disease and other hemoglobinopathies. Although testing is possible for many other disorders, Washington adds tests to the newborn screening panel only after careful consideration of the following criteria:

- **Prevention Potential and Medical Rationale:** Identification of the condition provides a clear benefit to the newborn - preventing delay in diagnosis; developmental impairment; serious illness or death.
- **Treatment Availability:** Appropriate and effective screening, diagnosis, treatment, and systems are available for evaluation and care.
- **Public Health Rationale:** Nature of the condition (symptoms are usually absent, such that diagnosis is delayed and treatment effectiveness is compromised) and prevalence of the condition justify population-based screening rather than risk-based screening.
- **Available Technology:** Sensitive, specific and timely tests are available that can be adapted to mass screening.
- **Cost-Benefit / Cost-Effectiveness:** Benefits justify the costs of screening.

Successful newborn screening requires collaboration between the State Newborn Screening Program, health care facilities (hospitals, local health departments, clinics), health care providers (pediatricians, family practice physicians, nurse practitioners, midwives), and families of newborns. The Washington State Newborn Screening Program is within the Department of Health and is located at the State Public Health Laboratories facility in Shoreline. It is a coordinated system of screening services comprised of laboratory, follow-up, and support staff.

Responsibilities of the Washington State Newborn Screening Program are:

- Ensuring rapid, efficient screening of children born in the state for the disorders required by state regulation (Chapter 246-650 Washington Administrative Code)
- Verifying that each newborn has had access to screening and if not, taking action to assure screening is available
- Providing appropriate follow-up and referrals to health care providers for newborns with abnormal screening test results to facilitate prompt diagnostic and treatment services.

- Consulting with health care providers regarding test implications and recommending follow-up actions
- Performing long-term follow-up and tracking of affected children to evaluate outcomes of the program, improve effectiveness and promote continued access to appropriate specialty health care
- Collecting, analyzing, and disseminating data on newborn screening requirements, including cost effectiveness of the system and health outcomes
- Consulting, providing technical assistance, and education regarding all components of newborn screening to hospitals, health care professionals, families of affected children, and the general public

Responsibilities of the health care facilities and providers are:

- Proper collection, labeling, and handling of newborn screening specimens.
- Documentation of the screening status of each infant.
- Quick response to information and specimen requests from the Newborn Screening Program.
- Prompt follow-up on infants requiring further testing to rule out or confirm a diagnosis.
- Provision of parent education about newborn screening and referrals to diagnostic and clinical care services as needed.

Responsibilities of the families are:

- Educating themselves about the newborn screening tests that will be performed on the infant.
- Reporting to the health care provider the presence of a family history of any screened or unscreened disorder.
- Responding quickly to requests from the health care provider or Department of Health for repeat screening.
- Working cooperatively with health care providers and institutions when required for follow-up.

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Responsibility for Obtaining a Newborn Screening Specimen

State law requires that every newborn be tested prior to discharge from the hospital or within five days of age. The law requires hospitals providing birth and delivery services or neonatal care to inform parents or other responsible parties about newborn screening, including the legal requirement and the right to refuse (see next section). These facilities are then required to collect a specimen, or signed refusal, to submit to the Newborn Screening Program. We recommend that physicians, midwives, and childbirth centers that deliver babies out-of-hospital follow the same guidelines as hospital births.

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Parental Right to Refuse

According to state law (Chapter 70.83 RCW - PHENYLKETONURIA AND OTHER PREVENTABLE HERITABLE DISORDERS), a newborn screening specimen should not be obtained on any newborn infant “whose parents or guardians object thereto on the grounds that such tests conflict with their religious tenets and practices”. If parents do refuse, it is the responsibility of the health care facility to obtain the signature from the parent(s) on the reverse side of the screening card to document the refusal. The provider must make certain that the parent(s) understand the risks of refusing the screening. As with collected specimens, the demographic information should be completed and the signed card forwarded to the Newborn Screening Program within 24 hours. The refusal should be noted in the infant’s medical record.

It is important to note that religious reasons are the only valid basis for refusal. Newborn screening statistics indicate that the majority of infants whose parents signed a refusal in the hospital were later tested, indicating that the initial refusal was not truly based on religious principles. This unacceptable practice could result in a delayed diagnosis for an affected infant and place them at significant risk of permanent damage or possibly death. The risk of refusal should be made clear to parents, and refusals should not be accepted for any reason except as allowed by law.

Aside from the fact that the hospital pre-discharge screen is mandated by state law, the practice of forgoing the first screen with the intent to collect a specimen at a later date is dangerous, placing the child at risk of delayed diagnosis and treatment of life threatening disorders.

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Timing of Screening

We recommend that the first newborn screening specimen be collected between 24 and 48 hours of age. In addition to the required first specimen, it is strongly recommended that every baby born in Washington have a second screening specimen submitted. If possible, this second specimen should be collected between 7 and 14 days of age. This recommendation has been carefully considered relative to the specific disorders included in Washington’s Newborn Screening Program. Laboratory detection of each of the ten disorders has its own special considerations related to the ideal time for testing, hence the recommendation for the timely collection and submission of two specimens. Both the first and second dried blood specimens receive the same battery of tests. The first screen is essential for making an early diagnosis to prevent life threatening events such as a salt-wasting crisis in a child with CAH, a fatal bacterial infection in a baby with galactosemia or a fatal metabolic crisis in a baby with MSUD. The second specimen optimizes detection of all of the disorders and is especially important for cystic fibrosis, homocystinuria and congenital hypothyroidism.

Due to the continuing trend of early hospital discharge, the first well-baby visit with the primary health care provider is also being scheduled earlier. The standard of care for

collecting the second specimen is still 7-14 days. However, in view of the increasing frequency of earlier first visits and possible uncertainty that the child will not be seen during the 7-14 day period, we are now recommending obtaining blood for the second newborn screen at the first well-baby visit, provided it is at least 48 hours after collection of the first specimen.

A third specimen at one month of age is recommended for sick and premature infants. [Click here](#) to download a one page synopsis of special considerations for NICU and Special Care Nurseries.

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Completing the Specimen Card

It is extremely important that all requested information on the specimen card be filled out completely and accurately. This information is critical to interpreting the test results and facilitating rapid communication of results back to the submitter and to the baby's primary care provider, if the results indicate the need for follow-up testing. Please contact the Newborn Screening Program at (206) 418-5410, 1-866-660-9050 (toll free) or NBS.Prog@doh.wa.gov to order specimen cards free of charge. A pamphlet for parents and a mailing envelope is also provided with each specimen card ordered.

Print all information using black ink. Try to avoid touching the filter paper while completing the form as this could affect the results. A copy of the current card is below:

SEE DIRECTIONS ON BACK: PLEASE PRINT.

DO NOT USE THIS AREA

NEWBORN SCREENING
WASHINGTON STATE DEPT. OF HEALTH
P.O. BOX 55729 (1610 NE 150TH ST)
SHORELINE, WA 98155-0729 www.doh.wa.gov/nbs
Phone: 206-418-5410 Toll Free: 1-866-660-9050

MOTHER'S INFORMATION

LAST NAME: _____

FIRST NAME: _____

MISCELLANEOUS INFORMATION

SUBMITTER INFORMATION

COLLECTED AT: _____

ID: _____

OUTPATIENT PROVIDER INFORMATION

WELL-CHILD CARE WITH: _____

ID: _____

CHILD'S INFORMATION

Birth: Mo Day Yr Hr : Mn am pm

Collection: _____

Name: First Last

Med Rec #: _____

Sex: M ☐ F ☐ Twin: A ☐ B ☐ C ☐ etc ☐

Birthweight: _____ grams

Race: White ☐ Black ☐ Asian ☐ NaAm ☐ Other ☐

Hispanic: Y ☐ N ☐

SPECIAL CONSIDERATIONS

NICU ☐ HATPN ☐ Steroids ☐ Antibiotics ☐

Transfused ☐ (date last) _____

IF TEST IS REFUSED BY PARENT, CHECK HERE (SIGNATURE IS REQUIRED ON BACK OF FORM)
DOI: 04/001 (REV 04/08)

Barcode: XXXXXXXX X

Right Side Labels: Ani from 226, Lot 804/201, XXXXXXXX, 84

Right Side Instructions: FILL EACH CIRCLE COMPLETELY BEFORE MOVING TO THE NEXT

Numbered Arrows:

- 1: LAST NAME
- 2: COLLECTED AT
- 3: WELL-CHILD CARE WITH
- 4: Collection
- 5: Birthweight
- 6: Race
- 7: Antibiotics
- 8: Signature line

Order cards [online](http://www.doh.wa.gov/ehspl/phl/newborn/order-form.htm) @ <http://www.doh.wa.gov/ehspl/phl/newborn/order-form.htm>

While all fields of the newborn screening card are important, we have noticed problems with compliance in the following areas as numbered above.

- 1 The mother's first and last names are used to link the first and second newborn screening specimens at the Newborn Screening Program. This linking may not occur if this information is different on the two specimen cards. Without this linkage, the Newborn Screening Program may contact the health care provider unnecessarily to collect an additional specimen. Please be sure to use the mother's last name in this section if mother and child have different last names. If the mother's name is too long to fit into the boxes provided, continue printing the name outside of them.
- 2 The submitter listed on the specimen card is the health care facility or provider that collected the specimen and will receive the results after screening. Please write both the full name and the ID number. The ID numbers for hospitals are listed on the back of the screening card. For other ID numbers please see our [Provider Directory webpage](#), or contact our office at (206) 418-5410, 1866-660-9050 (toll free) or NBS.Prog@doh.wa.gov.
- 3 Rapid follow-up of an abnormal screening test depends upon identifying the health care provider caring for the child. This provider should be the one who will see the child for primary care, such as a pediatrician, rather than the provider who cared for the child after birth, such as a hospitalist or neonatologist. Every effort should be made to ensure that the primary health care provider's information is accurate and complete. Please list both the name and the ID number of the provider. Please contact our office at (206) 418-5410, 1-866-660-9050 (toll free) or NBS.Prog@doh.wa.gov if you are not certain of your provider number. Some providers do not have an ID number (i.e. medical residents or fellows). In this case, please write the name of the facility where follow-up care will be provided in either this section or the Optional Use section.
- 4 The age of the infant at the time of collection is very important to correctly interpret the screening results. The date of birth and date of collection should include the month, day, and year as well as the time of day.
- 5 Birth weight is also important to correctly interpret the screening results. It should be entered in grams. Please indicate the weight of the child at birth, NOT the weight of the child at the time of specimen collection.
- 6 For the child's race, check all that apply. Include Aleut and Eskimo under Native American and all of the following under Asian: Asian Indian, Cambodian, Filipino, Guamanian, Hawaiian, Japanese, Korean, Laotian, Samoan, and Vietnamese. The guidelines for assigning race are also listed on the back of the newborn screening collection card. In addition to race, please indicate whether or not the child is of Hispanic ethnicity.
- 7 Transfusion can significantly affect the screening results, particularly for galactosemia and hemoglobinopathies. If the child has had a transfusion, please indicate this on the card and record the date of the most recent transfusion. When this box is checked, the

screening results for hemoglobin and galactosemia may be invalid. See [transfusions](#) for more information on how transfusion status affects screening.

- 8 If a parent or guardian refuses the newborn screening test, please check the box at the bottom of the card and have the parent or guardian sign the back of the card. In this case, please complete the demographic information on the card as you would if blood had been collected. See [parental right to refuse](#) for more information.

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Specimen Collection

The blood collection instructions described below are based on the approved standard published by the Clinical and Laboratory Standards Institute (CLSI). This was formerly NCCLS - National Committee for Clinical Laboratory Standards.) We have a video produced by this organization that is available for loan. If you would like to borrow the video or have questions regarding other blood collection techniques, please contact us at (206) 418-5410, 1-866-660-9050 (toll free) or NBS.Prog@doh.wa.gov (email).

The following equipment will be needed for specimen collection: a sterile, disposable lancet with a depth less than 2.0 mm, a sterile 70% isopropyl alcohol pad, sterile gauze, a soft cloth, the blood collection form, and gloves.

Gloves should be worn for personal safety. To prevent specimen contamination, do not touch the blood collection filter paper circles with gloved or ungloved hands, alcohol, formula, water, powder, antiseptic solution, lotion, or other substances.

After confirming the identity of the infant, place the infant's feet lower than the level of its heart in order to increase blood flow to the foot. To increase the blood flow at the puncture site, warm the heel for three to five minutes using a moist towel at a temperature no greater than 41°C. (Temperatures greater than this can burn the infant's skin.)

Select the puncture site. This should be the lateral or medial plantar surface of the heel, illustrated below. Do not use previous puncture sites or the area at the heel curvature. The puncture must not be performed on the central area of the foot. This may result in damage to the nerves, tendons, and cartilage of the foot.

Cleanse the puncture site with the sterile alcohol pad and allow the heel to air dry. Using the sterile lancet, perform a swift clean puncture. Wipe away the first drop of blood with a sterile gauze pad. Allow another large drop of blood to form. To enhance blood flow, apply very gentle intermittent pressure with the thumb to the area surrounding the puncture. Avoid excess squeezing or "milking" as it contaminates the blood sample with tissue fluid.

Lightly touch the blood drop to the filter paper circle and allow a sufficient quantity of blood to soak all the way through the paper to completely fill the circle. Do not press the paper against the puncture site. Apply blood to one side of the filter paper only and allow

full saturation before continuing with the next circle. Repeat this until all circles are filled. Do not apply successive drops of blood to the same circle. If a circle cannot be filled due to diminished blood flow, repeat the procedure on a new circle. It is important that complete saturation occur for each circle due to the quantitative measurements used during screening. Results are based on a specific blood quantity within a particular sized sample. When blood does not soak completely through, the results are not comparable to lab standards and will be returned to the submitter as unsuitable.

After blood collection, elevate the foot above the body and gently press the puncture site with a sterile gauze pad or cotton swab until the bleeding stops.

Although the heel stick procedure is preferable, use of sterile heparinized capillary tubes) for blood collection is acceptable (however, EDTA or citrate are unacceptable and will invalidate some test results). Follow the above procedures and apply approximately 75-100 ml to each circle, using a new tube for each circle. Touch the tube to the formed blood drop and make a single application immediately to the paper. Do not touch the capillary tube to the filter paper when applying the blood: this can scratch or abrade the sample invalidating it for screening.

Blood collection from the dorsal hand vein is also an acceptable blood collection technique. However, do not use a vein into which IV fluids or blood are being, or have been, infused since this will contaminate the specimen. After venipuncture, follow the step outlined above for the heel puncture.

The posters linked below can be ordered for your office by contacting us.

[Click here to view a poster of these procedures.](#)

[Click here to view a poster on specimen acceptability.](#)

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Shipping Samples

Allow the blood to air-dry on a flat, clean non-absorbent open surface for at least three hours at ambient temperature. Place the specimen so that the blood spots do not touch the surface; a test tube rack can make a nice drying platform. Keep the specimen away from direct heat, sunlight, or high humidity and do not refrigerate the specimen. Do not store in a plastic bag as this invalidates the specimen due to unknown effects of condensation and degradation of the blood. When completely dry, merely fold (do not tape or staple) the flap with the biohazard label over the blood circles and double check that all information has been completed.

Place the card into the envelope provided. If sending more than one specimen, we recommend using an envelope for each card; otherwise, alternate the cards so that the blood specimens do not come into contact with one another. (Do NOT place more than six collection cards in a single envelope.)

As required by law, send specimens to the Newborn Screening Laboratory within 24 hours of collection. Do not “batch” specimens from several days as this can significantly delay

diagnosis of an affected child and may result in specimens being too old to provide reliable results when they arrive.

For high priority specimens (i.e., infants suspected to have one of the conditions screened), overnight shipment is available via Federal Express. Call us at (206) 418-5410, 1866-660-9050 (toll free) or NBS.Prog@doh.wa.gov to arrange for this shipping.

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Responding to Results

Screening results will be sent to the submitter of the specimen. These results are to be used as a record for the child's medical chart. Please carefully read the results for each child to verify that the specimen was suitable for testing and that no further testing is necessary. This information should ideally be forwarded to the child's health care provider, especially if the results were abnormal or unsuitable.

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Requesting Results

If the results are not received for a specimen that you submitted within three weeks, please contact the Newborn Screening Program at (206) 418-5410, or fax your request to (206) 418-5415. Before calling, however, please verify that the results have not been misfiled, for example, under the mother's name.

If you are requesting results for a specimen that you did not submit, i.e., to verify that a first or second test has been done, please contact the health care facility or provider that submitted the specimen, if known, prior to contacting the Newborn Screening Program.

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Reporting Results

Screening results fall within three broad categories: normal, abnormal, and specimen unsuitable. Over 90% of the results will be mailed within five days of receipt; over 99% will be mailed within seven days. These results will be sent to the submitter of the specimen. If you receive a result report or letter that does not belong to a patient within your facility, please mail or fax the results to the Newborn Screening Program indicating such (fax: 206-418-5415).

Normal Results

Normal results will be sent to the submitter to be placed in the child's medical record. It is important to note that normal findings on the first test should not prevent a second specimen from being collected. As previously mentioned, the first screen is essential for making an early diagnosis necessary to prevent salt-wasting crisis in a child with CAH, a fatal bacterial infection in a baby with galactosemia or a fatal metabolic crisis in a baby with MSUD, and the second optimizes detection of all of the disorders. **IMPORTANT:** if a child

with normal newborn screening results develops clinical symptoms, the screening results should not prevent further testing.

Abnormal Results

Abnormal screening results include borderline and presumptive positive. The Newborn Screening follow-up staff tempers the response to abnormal test results by factors likely to influence the test results. For instance, abnormal results are often secondary to prematurity or early sampling (<24 hours of age). A second specimen is usually all that is required to rule out the presence of one of the disorders screened.

For borderline levels or hemoglobin trait results, results are mailed to the submitter with a request for a follow-up screen. If a second specimen is not received within two to four weeks, the child's primary health care provider will be contacted.

In the event of significant abnormal results, such as presumptive positive levels or a clinically significant hemoglobin disorder, the primary health care provider (as indicated on the screening card or by Medical Records where the child was born) is immediately contacted and appropriate recommendations for further testing are made. This may involve submitting another newborn screening specimen or following up with diagnostic testing and referral to a medical specialist. All abnormal results are also reported by mail to the submitter with a note indicating the recommended follow-up actions.

Unsuitable Specimens

Specimens can be unsuitable for testing for a variety of reasons. When possible the laboratory will test unsuitable specimens for extreme values, however, improper collection compromises the accuracy of the test results. This delays proper screening of the newborn and requires that a repeat specimen be submitted as soon as possible. Please see the [specimen acceptability page](#) for the various causes of unsuitable specimens.

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Report Format

The linked Acrobat pdf file contains an example of the format in which results are mailed to submitters upon completion of testing.

(Click here to view sample report)

- The first page is an address cover sheet. It may contain an important message from the screening program about a recent change in reporting or follow-up recommendation.
- The second page contains the results for an individual child. The State lab number for that child is listed on the top left and is followed by the demographic information as completed on the newborn screening card by the submitting facility. The next section contains the screening results for all disorders tested, including the laboratory result and the classification.
- The third page contains more detailed information only for specimens with abnormal or unsuitable results. It may contain further interpretation of the result, recommendations for follow-up, and actions taken by the Newborn Screening staff. It is important that this page be stored with the results on the previous page.

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Program Requests for Repeat Screening

When necessary, the Newborn Screening Program contacts health care providers to advise the need for a repeat specimen. This will occur, for example, if a previous specimen was unsuitable for screening or if there was a previous abnormal test result. This does not mean that the child has one of the disorders screened, but that another specimen is needed to evaluate the child's status. If you receive a request for another specimen, please contact the parent or guardian as soon as possible to help facilitate this.

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Program Requests for Information

The Newborn Screening Program sometimes receives screening cards with incomplete demographic information required for follow-up, such as the name of the primary care provider. To obtain this information, the hospital or other known health care provider is contacted. The information that is provided is kept confidential, as is the information on the screening card. Prompt responses to requests for information are appreciated.

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Transfusions

The first newborn screening specimen should be obtained prior to transfusion whenever possible. Specimens collected following red blood cell transfusions will yield invalid results for galactosemia and hemoglobinopathy screening. In the event that the first screening specimen is collected after a transfusion, please note this on the screening card. The galactosemia status and hemoglobin phenotype can be determined after the transfused cells have cleared. A specimen collected four to six weeks after the last transfusion will resolve galactosemia disease status and hemoglobin phenotype in most circumstances. The first and second specimens should still be collected within the recommended times because the detection of the other eight disorders is not affected by transfusions.

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Premature Infants and Sick Infants

The Washington State Newborn Screening Program recommends that all infants weighing less than 1500 grams at birth and sick infants requiring a hospital stay of three weeks or more have three specimens collected. The first prior to five days of age, the second at 7-14 days and the third between four to six weeks of age, or prior to discharge. Recent studies and our own experience in Washington State indicate that premature and sick infants with congenital hypothyroidism can have a late onset of thyroid stimulating hormone (TSH) elevation that is

not detected on the earlier specimens. It is thought that this delay may be caused by immaturity of the thyroid gland or receipt of transfusions and medications. There is no extra charge for the additional specimen; our one-time fee covers all testing that may be needed. [Click here](#) to download a one page synopsis of special considerations for NICU and Special Care Nurseries.

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Transferred Infants

As the hospital of birth is legally responsible for the screening, that hospital should ensure that the new facility is aware of the screening status. This should be documented in the infant's records at transfer. If there is no record of screening, a specimen should be obtained as soon as possible. This also applies to infants who are transferred to or from a hospital outside of Washington State.

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Parents Who Do Not Reside in Washington State

If an infant will not reside in Washington State after discharge from a Washington hospital, it is important that this be noted on the newborn screening card in the Optional Use section. Please also include the name and facility of the follow-up provider.

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Adoptions

For babies being adopted, please indicate the adoption agency or the infant's adoptive name (if known) on the newborn screening specimen card so they can be contacted if follow up is necessary. This information can be noted in the Optional Use section of the screening card. This also expedites follow up when the first test has the biological mother's name and the second has the adoptive mother's name. Without this information the two tests would not be linked and would be treated as two different infants. Information on adoptions will be kept confidential as is all information provided to the Newborn Screening Program.

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Infants with Clinical Signs of the Disorders Screened

As with all laboratory testing, newborn screening may yield false negative results. Regardless of the results of the newborn screen, the child's health care provider should proceed with diagnostic testing on any infant exhibiting clinical signs and symptoms. Please alert the Newborn Screening Program in this situation.

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Infants with Family History of the Disorders Screened

For any infant with a relative affected by one of the newborn screening disorders, please alert the Newborn Screening Program so testing can be expedited. In addition, please contact an appropriate medical specialist, ideally prenatally, to determine if any diagnostic testing or genetic counseling is indicated.

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Screening Older Children

Some children are not tested at birth, including those who immigrate into the United States. In addition, there may be children for whom screening status is not known, including children adopted from another state. We recommend that a specimen be obtained for these children at the first provider visit. Screening older children is valid for most of the disorders. It is very important that the date of birth be written on the card so that the results may be correctly interpreted. Please indicate the immigration or adoption status in the Optional Use section.

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Screening for Disorders Not Detected in Washington's Panel

As previously mentioned, there are other disorders that may be screened for at birth that are not included in the Washington State newborn screen. If the family is interested in obtaining expanded newborn screening beyond what we offer, there are laboratories that will perform testing on specimens for a fee. Pediatrix Screening (866-463-6436), Baylor University Medical Center (800-422-9567), Mayo Medical Clinic (800-533-1710) and University of Colorado (303-315-7301) will perform supplemental screening for over 20 metabolic disorders using a kit ordered by providers or parents. Please contact them, ideally prenatally, for further information.

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Storage of Newborn Screening Card

The Newborn Screening Program retains the specimen card for 21 years after the birth of the child. We retain these forms as a part of the child's health care records consistent with requirements for hospital records for minors. As health care information, the specimens and associated information are protected by HIPAA and cannot be used for purposes other than newborn screening except as allowed by law (Chapter 70.02 Revised Code of Washington, Medical Records - Health Care Information Access and Disclosure). Such uses have included testing the specimen for a disease diagnosed in the child later in life. For more information on this issue please see the [NBS Privacy Policy page](#).

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Newborn Screening Fee

The Newborn Screening Program is a self-supporting fee based program. A fee is charged for each infant tested through birthing facilities. This is a one-time fee and is charged per infant screened, not per specimen. The fee funds all activities of this comprehensive program. Diagnostic testing, if necessary, will involve additional costs. For the current fee, please see the [NBS Home Page](#).

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ASA/CIT

Argininosuccinic acidemia (ASA) and Citrullinemia (CIT) are amino acid disorders affecting the urea cycle and caused by a deficiency of argininosuccinate lyase and argininosuccinic acid synthetase, respectively. Deficiency in either enzyme causes a build-up of citrulline and ammonia in the bloodstream. High ammonia levels in the blood are severely toxic to the brain and can lead to seizures, coma and death. Early detection and treatment can reduce the mortality and morbidity associated with these disorders. However, even with treatment, the clinical presentation of these conditions varies.

Clinical Outcomes

ASA/CIT has two forms: 1) A severe, early form that presents within 2 days to 5 months of age (frequently misdiagnosed as sepsis), and 2) A sub-acute, late form presents in adolescence and adulthood (the less severe course can make diagnosis difficult). Both forms may present with lethargy, feeding difficulties and vomiting. Seizures progressing to coma and death are typical in untreated patients. Even with early treatment, some patients may have progressive mental retardation depending on ammonia surges associated with metabolic imbalances, dietary protein load and intercurrent infections. The prognosis is generally better for the late-onset form than the early-onset form.

Etiology

Argininosuccinic acidemia is caused by a deficiency of argininosuccinate lyase enzyme and results in elevated plasma argininosuccinic acid, citrulline and ammonia levels. Citrullinemia is caused by a deficiency of argininosuccinic acid synthetase enzyme and results in elevated plasma citrulline and ammonia levels. Both disorders are inherited in an autosomal recessive fashion. The birth prevalence of ASA is 1:70,000 while that of CIT is 1:57,000.

Screening Test

Screening for these disorders is performed by tandem mass spectrometry (MS/MS). The primary analyte for both ASA and CIT is *citrulline*. If CIT is elevated, secondary markers are analyzed. Results are classified in the tables below.

Laboratory Result Classifications and Corresponding Follow-up Actions for Citrulline (ASA)

Normal Results (μmol/L)	Borderline Results (μmol/L)	Presumptive Positive (μmol/L)
age < 8 days		
Citrulline < 40	not all secondary markers* elevated	all secondary markers* elevated
	Citrulline ≥ 40	Citrulline ≥ 40
age ≥ 8 days		
Citrulline < 45	not all secondary markers* elevated	all secondary markers* elevated
	Citrulline ≥ 45	Citrulline ≥ 45
Follow-up Actions		
Results are mailed to submitter. No follow-up is required.	Health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.	Health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.

* normal ranges for secondary markers: cit/arg < 5.56, asa < 0.77 μmol/L and asa/arg < 0.15

Laboratory Result Classifications and Corresponding Follow-up Actions for Citrulline (CIT)

Normal Results (μmol/L)	Borderline Results (μmol/L)	Presumptive Positive (μmol/L)
Citrulline < 50	cit/arg < 5.56 *	cit/arg ≥ 5.56 *
	Citrulline ≥ 50	Citrulline ≥ 50
Follow-up Actions		
Results are mailed to submitter. No follow-up is required.	Health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.	Health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.

* secondary marker

Treatment

The best developmental outcomes are achieved by keeping ammonia concentrations less than 480 μmol/L. This is accomplished with a high-caloric, protein-restrictive diet, supplemented with arginine. Sodium phenylbutyrate is the drug of choice used to clear ammonia from the body. Treatment must begin immediately upon diagnosis before irreversible damage occurs. Liver transplant is a radical alternative therapy to the classical dietary and medical regimen. Ammonia concentrations in the blood are regularly measured to calculate the appropriate level of dietary restriction required for an individual to avoid symptoms without impairing growth and intellectual development. Treatment must continue throughout life and people with ASA and CIT should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. **Parents should always travel with a letter from the child's physician with treatment guidelines in any case that may necessitate hospital admission during an acute illness.**

Special Considerations

- Diagnostic work-up of ASA and CIT includes a plasma amino acid profile and urine organic acid analysis. Diagnostic testing is coordinated through the [biochemical genetics laboratory](#) at Children's Hospital and Regional Medical Center.
- General anesthesia should be avoided as this may cause elevated ammonia levels.
- Hyperammonemia is not specific to ASA and CIT. It may be seen transiently in newborns within the first 24 hours of life or may be associated with congenital Herpes Simplex virus (HSV) infection, or seen in other organic acid disorders.
- Late-onset cases of ASA/CIT are likely to be missed if blood is collected when the baby is less than 72 hours old.
- The adult-onset form is more common in Japan.

Homocystinuria

Homocystinuria is characterized by a defect in the metabolism of the amino acid methionine, usually due to a deficiency of the enzyme cystathionine β -synthase. If untreated, approximately 50% of those with homocystinuria die before the age of 25 years, typically from thromboembolic events. Developmental delay, mental retardation, psychiatric disturbances, seizures, displacement of the lens of the eye, nearsightedness, scoliosis and osteoporosis are also commonly present. Initial treatment of homocystinuria consists of providing the baby with a formula that does not contain methionine. A methionine-restricted cysteine-supplemented diet may be required throughout life and administration of vitamin B6 (pyridoxine) is also often prescribed. The birth prevalence homocystinuria in the United States is approximately 1 in 200,000.

Clinical Features

Infants with homocystinuria appear normal at birth and early symptoms of the disorder are indistinct. Delayed development is usually noticed before 3 years of age. Nearsightedness is the first sign of lens dislocation. Signs of homocystinuria are similar to that of Marfan syndrome. Besides ocular abnormalities, affected individuals also have tall, thin statures with long limbs, spidery fingers and pectus deformity of the chest. Mental retardation, psychiatric disturbances, and thinning and weakness of the bones are also common. Individuals frequently develop blood clots, which can cause life threatening thromboembolic episodes.

Etiology

Homocystinuria is commonly caused by a genetic deficiency in one of the enzymes needed to properly metabolize the amino acid methionine. At least nine genetic defects have been shown to disrupt the major pathway in which methionine is metabolized. Cystathionine β -synthase deficiency is the most common and results in high levels of serum methionine. Homocystinuria is inherited in an autosomal recessive fashion.

Laboratory Tests

Homocystinuria screening is done using tandem mass spectrometry (MS/MS). To measure the level of methionine in the blood. Results are classified as in the table below.

Laboratory Result Classifications and Corresponding Follow-up Actions for Homocystinuria

Analyte	Normal Results	Borderline Results	Presumptive Positive
Methionine (micro mol/L serum)	< 80	80 - 89	≥ 90
	Results are mailed to specimen submitter. No follow-up is required.	NBS waits for the routine second specimen. If not received within 2 to 4 weeks, health care provider is contacted. If second screen, call health care provider to request a third screen. Results are also mailed to submitter.	If first screen, health care provider is contacted by phone to recommend immediate second specimen. If second screen, immediate diagnostic testing is recommended. Results are also mailed to submitter.

Treatment

Treatment for homocystinuria varies, but usually consists of a methionine-restricted, cysteine-supplemented diet, folic acid supplements and, if effective, high doses of vitamin B6. Slightly less than 50% respond to vitamin B6 therapy and those that do, should continue throughout their life. Treatment appears to reduce the risk of thromboembolic episodes, seizures, and mental retardation and delays lens dislocation.

False Positive/Negative

Because Washington State just began screening for homocystinuria in June 2006, and because it is very uncommon, information about false positive and false negative rates are not yet available.

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Maple Syrup Urine Disease (MSUD)

Maple syrup urine disease (MSUD) is characterized by an inability to metabolize the branched-chain amino acids leucine, isoleucine and valine due to an enzyme deficiency in the branched-chain alpha-keto acid dehydrogenase complex. If untreated, the most severe form of MSUD can result in death within the first weeks of life. Less severe forms of MSUD will result in mental retardation and metabolic decompensation during times of stress. Treatment consists of a special diet low in leucine, isoleucine and valine. The birth prevalence MSUD in the United States is approximately 1 in 200,000.

Clinical Features

There are four general classifications used to describe the variants of MSUD: classic, intermediate, intermittent and thiamine-responsive. In the most common type, classic MSUD, infants appear normal at birth but develop symptoms within four to seven days. Symptoms include poor feeding and weight gain (failure to thrive), vomiting, lethargy, hypotonia or hypertonia and the characteristic maple syrup smell of their urine. Babies with classic MSUD will die within the first year of life if left untreated.

Etiology

MSUD is caused by a genetic deficiency of one of the enzymes involved in the branched-chain alpha-keto acid dehydrogenase complex, which is needed to metabolize the essential amino acids leucine, isoleucine and valine. It is inherited in an autosomal recessive fashion.

Laboratory Tests

The MSUD screening is done using a tandem mass spectrometry (MS/MS) to measure the levels of leucine, valine and alanine in the blood. Results are classified as in the table below

Laboratory Result Classifications and Corresponding Follow-up Actions for MSUD

Analyte	Normal Results	Borderline Results	Presumptive Positive
Leucine (micro mol/L serum)	If age < 5 days, < 300; if age ≥ 5 days, < 350	If age < 5 days, 300-349; any age > 350 if valine and leu:ala not elevated	Leucine ≥ 350, valine ≥ 300 and leu:ala ≥ 1.75
	Results are mailed to specimen submitter. No follow-up is required.	If first screen, health care provider is contacted by phone to recommend a repeat newborn screening specimen as soon as possible. If two abnormal screens, diagnostic testing is recommended. Results are also mailed to submitter.	Health care provider is called and immediate diagnostic testing is recommended. Results are also mailed to submitter.

Treatment

Treatment of MSUD involves dietary restriction of branched-chain amino acids and requires frequent dietary monitoring that must continue throughout life. Levels of plasma branched-chain amino acids are measured to calculate the appropriate dietary restriction required for an individual to avoid symptoms of MSUD without impairing growth and intellectual development. Glucose and insulin infusions are commonly given during episodes of acute metabolic decompensation.

False Positive/Negative

Because Washington State just began screening for MSUD in June 2006, and because it is very uncommon, information about false positive and false negative rates are not yet available

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Phenylketonuria (PKU)

Phenylketonuria (PKU) was the first disorder targeted by universal newborn screening. PKU is characterized by the inability to metabolize the essential amino acid phenylalanine due to the lack of the enzyme phenylalanine hydroxylase. If untreated, PKU results in severe neurological and developmental damage. Although the exact pathogenesis of the damage to the central nervous system is still not clear, it seems likely that an increased concentration of phenylalanine in the blood is associated in some way with the neurodegenerative effects. Treatment consists of a special diet low in phenylalanine. Affected infants develop normally with early identification and proper dietary management. The birth prevalence of PKU in the United States is approximately 1 in 10,000-25,000. In Washington State, there are, on average, seven infants with PKU detected each year.

Clinical Features

Infants with PKU appear normal at birth. The symptoms of untreated PKU develop gradually, so they may not be noticed until irreversible mental retardation has occurred. The most common symptoms of untreated PKU are the following: a “musty” odor to the skin and urine, increased muscle tone and tendon reflexes, an eczema-like rash, and progressive neurological damage. With early treatment virtually all symptoms of the disorder are eliminated.

Etiology

PKU is caused by a genetic deficiency in the enzyme phenylalanine hydroxylase, which metabolizes the common amino acid phenylalanine. It is inherited in an autosomal recessive fashion.

Laboratory Tests

The PKU screening is no longer performed by the bacterial inhibition assay developed by Dr. Robert Guthrie, commonly known as the “Guthrie test.” Screening is now done using a technology called tandem mass spectrometry (MS/MS). The levels of phenylalanine and tyrosine in the blood spot are measured by a tandem mass spectrometer. Infants are considered to have a presumptive positive test for PKU when they have blood phenylalanine levels of 240 micro mol/L (equivalent to 4 mg/dL) or more and a phenylalanine-to-tyrosine ratio (phe: tyr) of 2 or greater.

Laboratory Result Classifications and Corresponding Follow-up Actions for PKU

<i>Analyte</i>	Normal Results	Borderline Results	Presumptive Positive
Phenylalanine (micro mol/L serum)	<152 if age ≤ 24 hrs and phe:tyr ≥ 2 otherwise <180	152-179 if age ≤ 24 hrs and phe:tyr ≥ 2 otherwise 180-239	>180 if age ≤ 24 hrs and phe:tyr ≥ 2 otherwise >240
	Results are mailed to specimen submitter. No follow-up is required.	Health care provider is contacted by phone to recommend a repeat newborn screening specimen as soon as possible. Results are also mailed to submitter.	Health care provider is contacted immediately by phone to recommend a repeat newborn screening specimen and/or <i>diagnostic testing</i> as soon as possible. Results are also mailed to submitter.

Diagnostic Testing

A positive PKU screening result must be confirmed as part of a clinical evaluation before a diagnosis is made. Diagnostic testing for PKU is done at Children's Hospital and Regional Medical Center's Biochemical Genetics Laboratory in collaboration with the University of Washington PKU Program in Seattle (see the Links page for contact information). The child can go directly to Children's Hospital or a blood and urine sample can be sent to their Clinical Laboratory. If diagnostic testing is recommended, the Newborn Screening Program will provide details on how the blood and urine should be collected.

Treatment

Early and proper initiation of a low-phenylalanine diet will prevent the mental retardation that occurs in untreated PKU. Strict dietary restriction of natural protein is required to reduce high blood phenylalanine levels. This is accomplished by the intake of a special metabolic formula (i.e. Phenyl-Free®) supplemented by low-protein foods and avoidance of aspartame (NutraSweet®). Treatment should be started as soon as the diagnosis is confirmed and should be continued indefinitely to optimize normal physical and mental development. Ongoing medical management with regular monitoring of phenylalanine levels is provided by a multidisciplinary team at the University of Washington PKU Clinic. The staff consists of a pediatric biochemical geneticist, nutritionists, a social worker, and genetic counselor. The special metabolic formula is distributed by the Newborn Screening Program in collaboration with the PKU Clinic.

Maternal PKU

As stated above, treatment for PKU should be continued throughout one's life. Discontinuing or even relaxing the dietary protein restriction may result in the late onset of clinical symptoms. It is especially critical that women of childbearing age maintain very strict dietary control. Women with high levels of phenylalanine during pregnancy are at increased risk of fetal loss, fetal brain damage, and other birth defects. If blood phenylalanine levels can be kept very low prior to conception and throughout the entire pregnancy, damage to the fetus can be minimized or avoided. Offspring of women who have PKU may have a transient elevation of phenylalanine on their newborn screening test. This level will fall to normal within a few days, unless the child has PKU (a 1 in 200 chance).

False Negative/Positive

The false negative rate for PKU depends on the age at which the infant is screened. A small percentage will be missed if the screening is done very early (prior to 12 hours of age). In Washington State, approximately 96% of infants with PKU are detected on the first newborn screen.

Special Considerations

The PKU screening test may yield equivocal results for babies who have received hyperalimentation or other therapeutic infusions. The result will be reported as an "inconclusive" and a follow up screen will be recommended when treatment is concluded. Prior feeding is not necessary to detect PKU, contrary to the previously common belief that infants must have at least 24 hours of feeding before the PKU test is accurate,. The majority of affected infants will be detected on the first screen, although milder forms of PKU may not be detected until the second screen.

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TYR-I

Tyrosinemia type I (TYR-I) is an amino acid disorder caused by a deficiency of fumaryl acetoacetate hydrolase (FAH). Deficiency of this enzyme causes a build-up of tyrosine and succinylacetone in the bloodstream. This is severely toxic to the liver, kidneys, heart and the nervous system, which can lead to multi-organ failure, seizures, coma and death. Early detection and treatment can reduce the mortality and morbidity associated with this disorder. However, even with treatment, the clinical presentation of this condition varies.

Clinical Outcomes

TYR-I has two forms: 1) An early-onset form (which is more common) that presents within the first 3 months of age and 2) A late-onset form (which is less common) presents in older children and adulthood. Without early treatment, both forms may present with diarrhea, vomiting, poor weight gain, jaundice, enlarged liver, edema (swelling of the abdomen or feet), painful abdominal crises, irritability and a characteristic "cabbage-like" odor in the

skin and urine. Current treatment is highly effective in avoiding these clinical complications.

Etiology

TYR-I is caused by a deficiency of fumaryl acetoacete hydrolase enzyme and results in elevated tyrosine and succinyl acetone levels. It is inherited in an autosomal recessive fashion. The birth prevalence of TYR-I is approximately 1:100,000 in the U.S., however, it is more common in French Canadians.

Screening Test

Screening for these disorders is performed by tandem mass spectrometry (MS/MS). The most sensitive (and specific) primary marker for TYR-I is *succinylacetone*. If this is elevated, secondary markers are analyzed.

Laboratory Result Classifications and Corresponding Follow-up Actions for SUAC (succinylacetone)

Normal Results (µmol/L)	Borderline Results (µmol/L)	Presumptive Positive (µmol/L)
	Tyrosine < 209*	Tyrosine ≥ 209*
SUAC < 3.25	SUAC ≥ 3.25	SUAC ≥ 3.25
Follow-up Actions		
Results are mailed to submitter. No follow-up is required.	If first specimen, health care provider is contacted by phone to recommend a repeat newborn screening specimen as soon as possible. If second specimen, health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> .	Health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.

* secondary marker

Treatment

Treatment of TYR-I involves dietary restriction of proteins, particularly tyrosine and phenylalanine, through use of a special dietary formula. *2-nitro-4-trifluoromethylbenzoyl-1,3-cyclohexanedione* (NTBC), also known as Nitisinone (generic name) and Orfadin (brand name), is the drug of choice. Treatment must begin immediately upon diagnosis before irreversible damage occurs. Clinical monitoring of affected individuals is done by measuring plasma amino acids, albumin, succinylacetone and NTBC levels. Treatment must continue throughout life and people with TYR-I deficiency should receive

specialized treatment through a metabolic clinic that has experience in treating this disorder. **Parents should always travel with a letter of treatment guidelines from the child's physician in any case that may necessitate hospital admission during an acute illness**

Special Considerations

- TYR-II, TYR-III and the late onset form of TYR-I will most likely not be detected by newborn screening.
- False positive NBS results may occur due to a variety of factors, including specimens contaminated with EDTA, exposure to high temperature, lead exposure, and in patients with hereditary gamma-aminolevulinic acid dehydratase deficiency.
- Diagnostic work-up of TYR-I includes a plasma amino acid profile and urine succinylacetone analysis. Diagnostic testing is coordinated through the [biochemical genetics laboratory](#) at Children's Hospital and Regional Medical Center.
- False negative results can occur when specimens are obtained following a blood transfusion or when an immunoreactive enzyme is expressed.

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CUD

Carnitine Uptake Deficiency (CUD) is a fatty acid oxidation disorder characterized by a defect in the transport of carnitine. It is caused by a defect in the sodium-dependent organic cation transporter-1 (OCTN-1) enzyme. This enzyme is essential in the transport of carnitine to cardiac and skeletal muscles (which is important in fatty acid oxidation) and maintaining normal plasma carnitine levels. This condition can cause heart disease, mental retardation, developmental delay in both motor and cognitive functions, and possibly death. Early identification and treatment reduces the mortality and morbidity associated with CUD. Even with treatment, the clinical presentation of CUD varies.

Clinical Outcomes

The onset may occur during the first two years of life, the most vulnerable period for metabolic crises. An illness or period of fasting can precipitate a metabolic crisis. Acute episodes are associated with refusal to feed, vomiting, listlessness, and lethargy, progressing to coma and death if not managed aggressively. Cardiomyopathy, liver complications, mental retardation, developmental delay and muscle weakness may present later in life. With early detection and treatment, children with CUD often live healthy lives with normal growth and development.

Etiology

CUD is a defect in the transport of carnitine into the skeletal muscles, heart and kidneys, leading to an impairment of fatty acid oxidation. Normal carnitine transport is also essential

in renal reabsorption of carnitine to maintain normal plasma carnitine levels. CUD is inherited in an autosomal recessive fashion. The birth prevalence estimates range from 1:40,000 (in Japan) to 1:100,000 (in Australia). Prevalence rates in the USA and Europe have not been defined.

Screening Test

Screening for CUD is performed by tandem mass spectrometry (MS/MS). The primary marker is *free carnitine* (C0). If C0 is low, secondary markers are analyzed. Results are classified in the table below.

Laboratory Result Classifications and Corresponding Follow-up Actions for C0

Normal Results (μmol/L)	Borderline Results (μmol/L)	Presumptive Positive (μmol/L)
C0 > 8.0	C3 + C16 > 2.0 *	C3 + C16 ≤ 2.0 *
	C0 ≤ 8.0	C0 ≤ 8.0
Follow-up Actions		
Results are mailed to submitter. No follow-up is required.	If first specimen, follow-up waits for routine second specimen (no phone call to submitter). If second specimen, health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.	If first specimen, health care provider is contacted by phone to recommend a repeat newborn screening specimen as soon as possible. If second specimen, health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.

* secondary marker

Treatment

Treatment of CUD consists of avoiding fasting, dietary supplementation with carnitine and high-carbohydrate, low-fat meals. Treatment must begin immediately upon diagnosis before irreversible organ damage occurs. Treatment must continue throughout life, and people with CUD deficiency should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose support may be required. **Parents should always travel with a letter from the child's physician with treatment guidelines in any case that may necessitate hospital admission during an acute illness.**

Special Considerations

- Diagnostic work-up of CUD includes blood carnitine analysis. Diagnostic testing is coordinated through the [biochemical genetics laboratory](#) at Children's Hospital and Regional Medical Center.
- In some cases bacterial metabolism in the intestine results in carnitine degradation and production of trimethylamine (a non-toxic chemical with a very unpleasant odor). This responds well to oral therapy with metronidazole (an antibiotic effective against anaerobic bacteria).
- Administration of certain drugs such as valproic acid and other compounds like benzoic acid and pivalic acid can cause false positive test results.
- Other differential diagnoses for reduced plasma carnitine concentrations include: 1) patients with renal Fanconi's syndrome and 2) carnitine-free feedings in neonates on intravenous alimentation

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L C H A D & T F P

Long-chain hydroxy-acyl CoA dehydrogenase (LCHAD) deficiency and trifunctional protein (TFP) deficiency are inborn errors of fatty acid oxidation characterized by deficiencies in a multi-enzyme complex deficiency that results in failure to break down long-chain fatty acids for energy metabolism. These conditions can damage the heart, brain, kidneys and vision and can rapidly progress to death. Early identification and treatment reduces the mortality and morbidity associated with LCHAD and TFP deficiencies. Even with treatment, the clinical presentations of these disorders vary.

Clinical Outcomes

The clinical presentation of these disorders is classified into three groups:

1. A severe, neonatal cardiac form characterized by early onset of heart disease (cardiomyopathy) and sudden infant death. Even with early detection and treatment, only a few patients have survived due to multi-system involvement and recurrent metabolic crises.
2. A less severe form affecting the liver presents in the first month of life. It is characterized by failure to thrive, vomiting, episodes of low blood sugar levels, seizures, and lethargy. With early detection and treatment, survival rate is improved.
3. A later onset form is noted after childhood and generally presents with muscle pain and weakness induced by exercise and strenuous physical activities. In most patients, nerve sensations such as tingling precedes breakdown of muscle tissues. With early detection and treatment, symptoms can be preventable.

Etiology

LCHAD deficiency is caused by an isolated deficiency of the long-chain hydroxyl-acyl CoA dehydrogenase enzyme. TFP deficiency is caused by markedly reduced activity of a multienzyme complex (including long-chain hydroxy-acyl Co-A dehydrogenase and two other enzymes: long-chain enoyl Co-A hydratase and long-chain keto-acyl Co-A thiolase). These three enzymes play important roles in the fatty acid oxidation pathway that produces energy during periods of metabolic stress and glycogen depletion after prolonged fasting. They are both inherited in an autosomal recessive fashion. Their combined birth prevalence is approximately 1 in 105,000.

Screening Test

Screening for these disorders is performed by tandem mass spectrometry (MS/MS). The primary marker for LCHAD and TFP deficiencies is *3 hydroxy-hexadecanoylcarnitine (C16OH)*. If *C16OH* is elevated, secondary markers are analyzed. Results are classified as in the table below.

Laboratory Result Classifications and Corresponding Follow-up Actions for C16OH

Normal Results (μmol/L)	Borderline Results (μmol/L)	Presumptive Positive (μmol/L)
C16OH < 0.19	not all secondary markers* elevated	all secondary markers* elevated
	C16OH ≥ 0.19	C16OH ≥ 0.19
Follow-up Actions		
Results are mailed to submitter. No follow-up is required.	Health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.	Health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.

* normal ranges for secondary markers: C14 < 0.29 μmol/L, C14:1 < 0.6 μmol/L, C16 < 5.69 μmol/L, C16OH/C16 < 0.062, C18 < 1.73 μmol/L and C18:1 < 2.48 μmol/L

Treatment

Treatment of LCHAD and TFP deficiencies consists of avoidance of fasting with frequent high-carbohydrate, low-fat meals, and medium chain triglyceride (MCT) oil to replace long chain fatty acids. Treatment must begin immediately upon diagnosis before irreversible organ damage occurs. Oral carnitine supplementation and docosahexanoic (DHA) diet may also be prescribed. People with LCHAD or TFP deficiency should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose support

may be required. **Parents should always travel with a letter from the child's physician with treatment guidelines in any case that may necessitate hospital admission during an acute illness.**

Special Considerations

- Diagnostic work-up of LCHAD and TFP deficiencies includes a blood acylcarnitine profile and urine organic acid analysis. If these are abnormal, they are followed by enzyme studies in fibroblasts and DNA analysis. Diagnostic testing is coordinated through the [biochemical genetics laboratory](#) at Children's Hospital and Regional Medical Center.
- LCHAD deficiency in a fetus predisposes the mother to the gestational complications of HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome and AFLP (acute fatty liver of pregnancy). Prenatal molecular diagnosis is possible and valid in guiding the management of pregnancies in families with confirmed TFP and LCHAD deficiency.

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Medium-chain Acyl-CoA Dehydrogenase (MCAD) Deficiency

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is characterized by the inability to produce adequate amounts of an enzyme involved in the metabolism of medium chain fatty acids. Proper production of the MCAD enzyme is critical in the process of providing fuel for the body during periods of extended fasting and higher energy demands. If untreated, MCAD deficiency can lead to metabolic failure, seizures, coma and death. Treatment consists of avoiding fasting by eating frequent meals, reducing dietary fat, and carnitine supplementation. The birth prevalence of MCAD deficiency in the United States is approximately 1 in 20,000.

Clinical Features

Infants with MCAD deficiency appear normal at birth but often develop symptoms between three and 24 months of age in response to either prolonged fasting or common illness. However, without these environmental triggers survival can continue through adulthood. Clinical signs are variable and may be confused with other fatty acid oxidation disorders. Infants may present with hypoglycemia, vomiting, and lethargy, which may progress to seizures, coma, and sudden death. Hepatomegaly and acute liver disease are often present. Approximately 20% of those affected die during the first crisis.

Etiology

MCAD deficiency is caused by a genetic deficiency in the medium-chain acyl-CoA dehydrogenase enzyme, which results in a defect of fatty acid beta-oxidation, a major source of energy when the body's hepatic glycogen stores are depleted. MCAD deficiency is inherited in an autosomal recessive fashion.

Laboratory Tests

The MCAD deficiency screening is done using tandem mass spectrometry (MS/MS) to measure the levels of octanoyl carnitine (C8) and acyl carnitine (C2) in the blood. A second-tier test

will be performed on screen positive specimens if needed to further clarify the significance of the initial test results.

Laboratory Result Classifications and Corresponding Follow-up Actions for MCAD deficiency

<i>Analyte</i>	Normal Results	Borderline Results	Presumptive Positive
Octanoyl carnitine (micro mol/L serum)	<0.5	0.5-0.79	≥ 0.8
	Results are mailed to specimen submitter. No follow-up is required.	If first screen, health care provider is contacted by phone to recommend a repeat newborn screening specimen as soon as possible. If two abnormal screens, diagnostic testing is recommended. Results are also mailed to submitter.	If first screen, health care provider is contacted by phone to recommend immediate diagnostic testing. Results are also mailed to submitter.

Treatment

Treatment for MCAD deficiency is simple and appears to be very effective. Those affected need to avoid fasting by having frequent meals and limit their intake of medium- and long-chain fatty acids. In circumstances where food cannot be tolerated, such as during an illness, intravenous glucose support may be required. Carnitine supplementation is sometimes prescribed to correct for secondary carnitine deficiency and help eliminate toxic metabolites.

False Positive/Negative

Because Washington State just began screening for MCAD deficiency in June 2004, and because it is uncommon, information about false positive and false negative rates are not yet available.

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V L C A D

Very long-chain acyl CoA dehydrogenase (VLCAD) deficiency is an inborn error of fatty acid metabolism. It is caused by a deficiency in the very long-chain acyl CoA dehydrogenase enzyme which results in the failure to break down very long-chain fatty acids (12-18 carbon molecules) for energy metabolism. This condition can damage the heart, muscles and kidneys, and can cause seizures or death. Early identification and treatment reduces the mortality and morbidity associated with VLCAD deficiency. Even with treatment, the clinical presentation of VLCAD deficiency varies.

Clinical Outcomes

An infantile form of VLCAD deficiency is characterized by non-specific signs and symptoms such as irritability, decreased muscular activity and lethargy. The associated heart disease (cardiomyopathy) can eventually lead to death. With early detection and treatment, cardiomyopathy can be resolved and death can be prevented.

A later onset form of VLCAD deficiency is manifested by muscle pains and weakness, induced by strenuous physical activities or triggered by prolonged episodes of fasting. If detected early and treatment started, metabolic imbalances and complications to the kidneys can be prevented, however this form may not always be detected by newborn screening.

Etiology

Normal production and function of the VLCAD enzyme in the mitochondrial membrane is critical to the process of providing fuel for the body during periods of extended fasting and higher energy demands. VLCAD deficiency is inherited in an autosomal recessive fashion. The birth prevalence of VLCAD deficiency is approximately 1 in 121,000 births.

Screening Test

Screening for VLCAD deficiency is performed by tandem mass spectrometry (MS/MS). The primary marker for VLCAD deficiency is *tetradecenoylcarnitine (C14:1)*. If *C14:1* is elevated, secondary markers are analyzed. Results are classified as in the table below.

Laboratory Result Classifications and Corresponding Follow-up Actions for C14:1

Normal Results (μmol/L)	Borderline Results (μmol/L)	Presumptive Positive (μmol/L)
age < 8 days		
C14:1 < 0.6	not all secondary markers* elevated	all secondary markers* elevated
	C14:1 ≥ 0.6	C14:1 ≥ 0.6
age ≥ 8 days		
C14:1 < 0.35	not all secondary markers* elevated	all secondary markers* elevated
	C14:1 ≥ 0.35	C14:1 ≥ 0.35
Follow-up Actions		
Results are mailed to submitter. No follow-up is required.	Health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.	Health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.

* normal ranges for secondary markers: C14 < 0.29 μmol/L, C14:1/C16 < 0.13, C16 < 5.69 μmol/L, C18 < 1.73 μmol/L, C18:1 < 2.48 μmol/L

Treatment

Treatment of VLCAD deficiency consists of avoidance of fasting, with frequent high-carbohydrate, low-fat meals, and medium chain triglyceride (MCT) oil to replace long chain fatty acids. Treatment must begin immediately upon diagnosis before irreversible organ damage occurs. Oral carnitine supplementation may be necessary. People with VLCAD deficiency should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose support may be required. **Parents should always travel with a letter from the child's physician with treatment guidelines in any case that may necessitate hospital admission during an acute illness**

Special Considerations

- Diagnostic work-up of VLCAD deficiency includes a blood acylcarnitine profile and urine organic acid analysis. If these are abnormal, they are followed by enzyme studies in fibroblasts. Diagnostic testing is coordinated through the [biochemical genetics laboratory](#) at Children's Hospital and Regional Medical Center.

- The C14:1 marker may also be elevated in carnitine palmitoyl transferase (CPT) deficiency, multiple acyl CoA dehydrogenase (MAD) deficiency and long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD) deficiency.
- Administration of certain drugs such as valproic acid, antibiotics containing pivalic acid, and other compounds like benzoic acid and can cause false positive results.
- Screening for VLCAD deficiency is optimal in the first seven days of life because acylcarnitine levels rapidly decrease with time. VLCAD deficiency may be missed if the child is screened beyond 7 days of age. Therefore, a mutation analysis should be done if an older baby is clinically symptomatic or the medical provider is considering VLCAD deficiency as one of differential diagnoses (based on a positive family history) to help confirm or rule out the diagnosis.

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HMG Deficiency

3-hydroxy-3-methyl glutaryl CoA lyase (HMG) deficiency is an organic acid disorder characterized by the inability to process the amino acid leucine due to lack of the 3-hydroxy-3-methyl glutaryl CoA lyase enzyme. This condition can cause damage to the brain that may lead to death. Early identification and treatment reduces the mortality and morbidity associated with HMG deficiency. Even with treatment, the clinical presentation of HMG deficiency varies.

Clinical Outcomes

Acute episodes are associated with vomiting, decreased muscle tone or activity, and lethargy. An illness or period of fasting can precipitate a metabolic crisis manifested by hypoglycemia and can lead to death. With early detection and treatment, the child has a better chance of normal neurodevelopmental outcomes.

Etiology

HMG deficiency is a very rare condition caused by a deficiency of the 3-hydroxy 3-methyl glutaryl CoA lyase enzyme, which disrupts the normal metabolism of leucine. It is inherited in an autosomal recessive fashion. The birth prevalence of HMG deficiency is unknown.

Screening Test

Screening for HMG deficiency is performed by tandem mass spectrometry (MS/MS). The primary marker for HMG deficiency is *3-hydroxy-isovaleryl carnitine (C5-OH)*. If *C5OH* is elevated, secondary markers are analyzed. Results are classified as in the table below.

Laboratory Result Classifications and Corresponding Follow-up Actions for C5OH (HMG)

Normal Results (μmol/L)	Borderline Results (μmol/L)	Presumptive Positive (μmol/L)
C5OH < 0.6	C5OH/C8 < 8.5*	C5OH/C8 ≥ 8.5*
	0.6 ≤ C5OH ≤ 4.0	0.6 ≤ C5OH ≤ 4.0
	Special Circumstance - Probable 3MCC	
	any C5OH > 4.0	
Follow-up Actions		
Results are mailed to submitter. No follow-up is required.	<p>If first specimen, health care provider is contacted by phone to recommend a repeat newborn screening specimen as soon as possible. If second specimen, health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i>.</p> <p>Special Circumstance: If C5OH is greater than 4.0 μmol/L, the likelihood of HMG is very low. The probable reason for the elevation in C5OH is 3-methylcrotonyl carboxylase (3MCC) deficiency in the newborn or the mother. If a first specimen, the health care provider is contacted by phone to recommend a second newborn screen at two weeks of age. If a second specimen, the health care provider is contacted by phone to recommend <i>diagnostic testing</i>. Newborn screening results are also mailed to submitter.</p>	Health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.

* secondary marker

Treatment

Treatment of HMG deficiency involves avoiding fasting, with a high carbohydrate, low protein diet with restriction of leucine, through use of a special dietary formula. Leucine concentrations in the blood are regularly measured to calculate the appropriate level of dietary restriction required for an individual to avoid symptoms of HMG deficiency without impairing growth and intellectual development. Oral carnitine may be supplemented. Treatment must begin immediately upon diagnosis before irreversible damage occurs. Treatment must continue throughout life and people with HMG deficiency should receive specialized treatment through a metabolic clinic that has experience in treating this

disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose support may be required. **Parents should always travel with a letter from the child's physician with treatment guidelines in any case that may necessitate hospital admission during an acute illness.**

Special Considerations

Diagnostic work-up of HMG deficiency includes a blood acylcarnitine profile and urine organic acid analysis. Diagnostic testing is coordinated through the [biochemical genetics laboratory](#) at Children's Hospital and Regional Medical Center.

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BKT

Beta-ketothiolase (BKT) deficiency is an organic acid disorder characterized by the inability to process the amino acid isoleucine and fats due to lack of BKT enzyme. This condition can cause brain damage that may lead to death. Early identification and treatment reduces the mortality associated with BKT deficiency. Even with treatment, the clinical presentation varies.

Clinical Outcomes

The onset may occur during the first two years of life. Acute episodes are associated with vomiting, diarrhea, failure to thrive, and seizures. Intercurrent infections or increased protein intake can precipitate a metabolic crisis leading to coma and death if left untreated. The frequency of decompensation falls with age and is not common after the age of ten. With early detection and treatment, the child has a better chance of normal neurodevelopmental outcomes.

Etiology

BKT deficiency is a very rare condition caused by a lack of the BKT enzyme, which disrupts the normal metabolism of isoleucine and fats. It is inherited in an autosomal recessive fashion. The birth prevalence of BKT deficiency is unknown.

Screening Test

Screening for BKT deficiency is performed by tandem mass spectrometry (MS/MS). The primary marker for BKT deficiency is *3-methylcrotonyl carnitine (C5:1)*, also known as *tiglyl carnitine*. If *C5:1* is elevated, secondary markers are analyzed. Results are classified as in the table below.

Laboratory Result Classifications and Corresponding Follow-up Actions for C5:1

Normal Results (μmol/L)	Borderline Results (μmol/L)	Presumptive Positive (μmol/L)
C5:1 < 0.2	not all secondary markers* elevated	all secondary markers* elevated
	C5:1 ≥ 0.2	C5:1 ≥ 0.2
Follow-up Actions		
Results are mailed to submitter. No follow-up is required.	If first specimen, health care provider is contacted by phone to recommend a repeat newborn screening specimen as soon as possible. If second specimen, health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.	Health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.

* normal ranges for secondary markers: C5OH < 0.6 μmol/L and C5OH/C8 < 8.5

Treatment

Treatment of BKT deficiency involves avoiding fasting, with high carbohydrate, low protein diet with restriction of isoleucine, through use of a special dietary formula. Isoleucine concentrations in the blood are regularly measured to calculate the appropriate level of dietary restriction required for an individual to avoid symptoms of BKT deficiency without impairing growth and intellectual development. Oral carnitine may be supplemented. Treatment must begin immediately upon diagnosis before irreversible damage occurs. Families must be taught how to monitor urinary ketones to be alert for impending metabolic crisis. Treatment must continue throughout life and people with BKT deficiency should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose support may be required. **Parents should always travel with a letter from the child's physician with treatment guidelines in any case that may necessitate hospital admission during an acute illness.**

Special Considerations

Diagnostic work-up of BKT deficiency includes a blood acylcarnitine profile and urine organic acid analysis. Diagnostic testing is coordinated through the [biochemical genetics laboratory](#) at Children's Hospital and Regional Medical Center.

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GA-I Glutaric Acidemia Type I

Glutaric acidemia type I (GA-I) is an organic acid disorder characterized by the inability to process the amino acids lysine, hydroxylysine and tryptophan due to lack of the glutaryl co-A dehydrogenase enzyme. This condition can cause damage to the brain that may lead to death. Early identification and treatment reduces the mortality and morbidity associated with GA-I. Even with treatment, the clinical presentation of GA-I varies.

Clinical Outcomes

The most suggestive and earliest sign before a neuro-metabolic crisis occur is progressive macrocephaly (head circumference more than 95th percentile at birth). Typically between 2-18 months of age, a nonspecific illness such as a respiratory or gastro-intestinal infection, or even an adverse reaction to immunization may lead to an acute metabolic crisis progressing to neurologic complications. Early signs of an encephalopathic crisis include irritability, lethargy, and hypotonia (e.g. sudden head lag) which may progress to stupor and coma within hours. Hence, a metabolic decompensation must be treated aggressively to avoid permanent brain damage. With early detection and treatment, neurodevelopmental complications can be prevented but for patients who are already neurologically impaired, this can minimize brain damage.

Etiology

GA-I is caused by a deficiency in the glutaryl Co-A dehydrogenase enzyme. This enzyme is active in the liver, kidneys, fibroblasts and leukocytes and helps break down lysine, hydroxylysine and tryptophan. GA-I is inherited in an autosomal recessive fashion. The birth prevalence of GA-I is approximately 1 in 137,000.

Screening Test

Screening for GA-I is performed by tandem mass spectrometry to measure the levels of *glutaryl carnitine (C5DC)* in the blood. If *C5DC* is elevated, secondary markers are analyzed. Results are classified as in the table below.

Laboratory Result Classifications and Corresponding Follow-up Actions for C5DC

Normal Results (μmol/L)	Borderline Results (μmol/L)	Presumptive Positive (μmol/L)
C5DC < 0.23	not all secondary markers* elevated	all secondary markers* elevated
	C5DC ≥ 0.23	C5DC ≥ 0.23
Follow-up Actions		
Results are mailed to submitter. No follow-up is required.	If first specimen, health care provider is contacted by phone to recommend a repeat newborn screening specimen as soon as possible. If second specimen, health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.	Health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.

* normal ranges for secondary markers: C5DC/C50H < 1.0, C5DC/C8 < 1.0 and C5DC/C16 < 0.08

Treatment

Treatment for GA-I involves dietary restriction of lysine, hydroxylysine and tryptophan, through use of a special dietary formula. Concentrations of these amino acids in the blood are regularly measured to calculate the appropriate level of dietary restriction required for an individual to avoid symptoms of GA-I without impairing growth and intellectual development. Treatment must begin immediately upon diagnosis before irreversible damage occurs. Treatment must continue throughout life and people with GA-I should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose and pharmacological doses of carnitine may be required. **Parents should always travel with a letter from the child's physician with treatment guidelines in any case that may necessitate hospital admission during an acute illness**

Special Considerations

- Diagnostic work-up of GA-I includes a blood acylcarnitine profile, urine organic acid analysis and urine acylglycine analysis. Diagnostic testing is coordinated through the [biochemical genetics laboratory](#) at Children's Hospital and Regional Medical Center.
- C5DC (glutaryl carnitine) is a secondary analyte for glutaric academia type II (also known as multiple acyl co-A dehydrogenase deficiency) and may be elevated as well in medium-chain acyl-CoA dehydrogenase (MCAD) deficiency.

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IVA

Isovaleric acidemia (IVA) is an organic acid disorder characterized by a deficiency of the isovaleryl Co-A dehydrogenase enzyme which is needed in the processing of the amino acid leucine. This condition can cause brain damage and rapidly progresses to coma and death from cerebral edema or hemorrhage. Early identification and treatment reduces the mortality and morbidity associated with IVA. However, even with treatment, the clinical presentation of IVA varies.

Clinical Outcomes

An acute form of IVA usually presents within the first 14 days of life. Acute episodes are associated with nonspecific signs and symptoms such as vomiting, irritability, seizures, and lethargy progressing to coma and death. A characteristic “sweaty feet odor” may also be noted. With early detection and treatment, infants can survive the neonatal period without serious complications or neurologic damage.

A later-onset form occurs in the first year of life and is often triggered by respiratory infections or excessive consumption of protein. It presents with failure to thrive and recurrent episodes of vomiting, lack of appetite and lethargy. With early detection and treatment, mental retardation, speech and other developmental delays can be avoided.

Etiology

IVA is caused by a deficiency of the isovaleryl Co-A dehydrogenase enzyme, which disrupts the normal metabolism of the amino acid leucine and results in the build up of isovaleric acid. It is inherited in an autosomal recessive fashion. The birth prevalence of IVA is approximately 1 in 96,000 births.

Screening Test

Screening for IVA is performed by using tandem mass spectrometry (MS/MS). The primary marker for IVA is *isovalerylcarnitine (C5)*. If *C5* is elevated, secondary markers are analyzed. Results are classified in the table below.

Laboratory Result Classifications and Corresponding Follow-up Actions for C5

Normal Results (μmol/L)	Borderline Results (μmol/L)	Presumptive Positive (μmol/L)
age < 8 days		
C5 < 0.55	not all secondary markers* elevated	all secondary markers* elevated
	C5 ≥ 0.55	C5 ≥ 0.55
age ≥ 8 days		
C5 < 0.55	not all secondary markers* elevated	all secondary markers* elevated
	C5 ≥ 0.75	C5 ≥ 0.75
Follow-up Actions		
Results are mailed to submitter. No follow-up is required.	If first specimen, health care provider is contacted by phone to recommend a repeat newborn screening specimen as soon as possible. If second specimen, health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.	Health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.

* normal ranges for secondary markers: C5/C0 < 0.02, C5/C2 < 0.02 and C5/C3 < 0.33

Treatment

Treatment of IVA involves dietary restriction of leucine, through use of a special dietary formula. Leucine concentrations in the blood are regularly measured to calculate the appropriate level of dietary restriction required for an individual to avoid symptoms of IVA without impairing growth and intellectual development. Oral glycine and carnitine may be supplemented. Treatment must begin immediately upon diagnosis before irreversible damage occurs. Treatment must continue throughout life and people with IVA should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose support may be required. **Parents should always travel with a letter from the child's physician with treatment guidelines in any case that may necessitate hospital admission during an acute illness**

Special Considerations

- Diagnostic work-up of IVA includes a blood acylcarnitine profile, urine organic acid analysis and urine acylglycine analysis. Diagnostic testing is coordinated through the [biochemical genetics laboratory](#) at Children's Hospital and Regional Medical Center.
- Aspirin and benzoic acid will block the beneficial effects of glycine, and should be avoided.

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MMA/PA

Methylmalonic acidemias (MMA) and propionic acidemia (PA) are organic acid disorders caused by mutations in the genes encoding methylmalonyl Co-A mutase and propionyl Co-A carboxylase, respectively. An isolated or combined deficiency of these enzymes causes a build-up of the amino acids isoleucine, valine, methionine and threonine. These amino acids are normally converted to succinyl Co-A, which is essential for energy production. The metabolic imbalances can cause brain damage and rapidly progress to coma and death. Early detection and treatment reduces the mortality and morbidity associated with these disorders. However, even with treatment, the clinical presentation of these conditions varies.

Clinical Outcomes

The clinical presentation of these disorders is classified in two main groups:

- 1) An early onset, severe form is characterized by poor feeding, vomiting, dehydration, respiratory distress, lethargy, seizures, posturing or poor muscle tone. Acute episodes are usually precipitated by fever, vaccinations or intercurrent infections and can lead to death. It appears that early identification and treatment improves the survival rate. Many patients identified clinically showed poor nutritional status with growth retardation and neurologic impairment.
- 2) A late onset, milder form is often manifested by refusal to feed, vomiting, dehydration, respiratory distress, seizures, lethargy and can lead to death. It can be precipitated by excessive protein intake, fever or intercurrent infection. Despite adequate treatment, many MMA patients develop a progressive renal disease by adolescence or early adulthood and neurologic complications may be manifested. The milder forms have a better prognosis than the early-onset forms and patients will benefit from early detection and treatment through newborn screening.

Etiology

Methylmalonic acidemia is caused by a deficiency in either the methylmalonyl Co-A mutase enzyme or defects in the production of adenosyl cobalamin. Propionic acidemia is caused by a deficiency in the propionyl Co-A carboxylase enzyme. Both disorders are inherited in an

autosomal recessive fashion. The combined birth prevalence of MMAs and PA is approximately 1:48,000.

Screening Test

Screening for these disorders is performed by tandem mass spectrometry (MS/MS). The primary marker for methylmalonic acidemia and propionic acidemia is *propionylcarnitine* (C3). If C3 is elevated, secondary markers are analyzed. Results are classified in the table below.

Laboratory Result Classifications and Corresponding Follow-up Actions for C3

Normal Results (μmol/L)	Borderline Results (μmol/L)	Presumptive Positive (μmol/L)
age < 8 days		
C3 < 5.25	not all secondary markers* elevated	all secondary markers* elevated
	C3 ≥ 5.25	C3 ≥ 5.25
age ≥ 8 days		
C3 < 4.4	not all secondary markers* elevated	all secondary markers* elevated
	C3 ≥ 4.4	C3 ≥ 4.4
Follow-up Actions		
Results are mailed to submitter. No follow-up is required.	Health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.	Health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.

* normal ranges for secondary markers: C3/C2 < 0.17 and C3/C16 < 2.1

Treatment

The aim of treatment is to prevent damage to the brain and other vital organs (kidneys, heart, liver, pancreas) while maintaining normal development and nutritional status. This is accomplished by frequent feeding of high-energy, low-protein diet. Oral biotin, Vitamin B12, and L-carnitine may be supplemented. Avoidance of fasting is recommended. Treatment must begin immediately upon diagnosis before irreversible damage occurs. Treatment must continue throughout life and people with MMAs or PA should receive specialized treatment through a metabolic clinic that has experience in treating these disorders. In circumstances where food cannot be tolerated, such as during an illness, IV glucose or total parenteral nutrition (TPN) support may be required. **Parents should always**

travel with a letter from the child's physician with treatment guidelines in any case that may necessitate hospital admission during an acute illness.

Special Considerations

- The newborn screening profiles for MMA and PA can be very similar, so diagnostic testing is necessary to differentiate between the conditions. It includes a blood acylcarnitine profile, urine organic acid analysis, and plasma amino acid measurement. Diagnostic testing is coordinated through [biochemical genetics laboratory](#) at Children's Hospital and Regional Medical Center.
- Not all forms of MMA will be detected by newborn screening.
- Elevated C3 levels in newborns can be caused by maternal Vitamin B12 deficiency

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MCD

Multiple carboxylase deficiency (MCD) is an organic acid disorder caused by an inborn error of biotin metabolism. It is also known as holocarboxylase synthetase deficiency (HCSH). Biotin is a B-complex vitamin (also known as vitamin B₇ or vitamin H). It is essential in the metabolism of carbohydrates, proteins, and fats for energy production. Holocarboxylase synthetase catalyzes the transfer of biotin to four biotin-dependent enzymes, namely: 1) beta-methylcrotonyl Co-A carboxylase, 2) propionyl Co-A carboxylase, 3) pyruvate carboxylase, and 4) acetyl Co-A carboxylase. This condition can cause respiratory, skin, and neurodevelopmental problems. Even with treatment, the clinical presentation of MCD varies.

Clinical Outcomes

The onset may occur from birth to 15 months of age (in contrast to biotinidase deficiency which may occur later in infancy). An illness or period of fasting can precipitate a metabolic crisis. Acute episodes are associated with skin rashes, hair loss, vomiting, breathing problems, and seizures. If left untreated this may lead to poor growth, learning disabilities, and mental retardation. With early detection and treatment, the child has a good chance of normal neurodevelopmental outcomes.

Etiology

MCD is a very rare condition caused by a lack of the holocarboxylase synthetase enzyme, which disrupts the normal binding of biotin and, consequently, the metabolism of proteins, carbohydrates and fats. It is inherited in an autosomal recessive fashion. The birth prevalence of MCD is approximately 1:87,000.

Screening Test

Screening for MCD deficiency is performed by tandem mass spectrometry (MS/MS). The primary marker is *3-hydroxy-isovaleryl carnitine (C5OH)*. If *C5OH* is elevated, secondary markers are analyzed. Results are classified in the table below.

Laboratory Result Classifications and Corresponding Follow-up Actions for C5OH (MCD)

Normal Results (μmol/L)	Borderline Results (μmol/L)	Presumptive Positive (μmol/L)
C5OH < 0.6	not all secondary markers* elevated	all secondary markers* elevated
	$0.6 \leq C5OH \leq 4.0$	$0.6 \leq C5OH \leq 4.0$
	Special Circumstance - Probable 3MCC	
	any C5OH > 4.0	
Follow-up Actions		
Results are mailed to submitter. No follow-up is required.	<p>If first specimen, health care provider is contacted by phone to recommend a repeat newborn screening specimen as soon as possible. If second specimen, health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i>.</p> <p>Special Circumstance: If C5OH is greater than 4.0 μmol/L, the likelihood of HMG is very low. The probable reason for the elevation in C5OH is 3-methylcrotonyl carboxylase (3MCC) deficiency in the newborn or the mother. If a first specimen, the health care provider is contacted by phone to recommend a second newborn screen at two weeks of age. If a second specimen, the health care provider is contacted by phone to recommend <i>diagnostic testing</i>. Newborn screening results are also mailed to submitter.</p>	Health care provider is contacted by phone to recommend immediate <i>diagnostic testing</i> . Newborn screening results are also mailed to submitter.

* normal ranges for secondary markers: C5OH/C8 < 8.5 and C3 < 5.7 μmol/L

Treatment

Treatment of MCD involves avoiding fasting and prompt administration of biotin upon diagnosis to ensure normal growth and development. Treatment must begin immediately

upon diagnosis before irreversible damage occurs. Treatment must continue throughout life and people with MCD should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose support may be required.

Special Considerations

Diagnostic work-up of MCD includes a blood acylcarnitine profile and urine organic acid analysis. Diagnostic testing is coordinated through the [biochemical genetics laboratory](#) at Children's Hospital and Regional Medical Center.

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Biotinidase Deficiency

Biotinidase deficiency is characterized by an inability to recycle the vitamin biotin due to lack of the enzyme biotinidase. If untreated, profound biotinidase deficiency can lead to irreversible neurological damage, metabolic crisis and even death. Partial deficiency of the enzyme has far less effect. Treatment consists of oral doses of the unbound form of the vitamin biotin; typically 10 mg per day. Bound biotin as found in over the counter vitamin supplements is not effective because biotinidase enzyme is needed to process it. Early diagnosis and proper treatment will avoid all damage from either form. The birth prevalence of profound biotinidase deficiency in the United States is approximately 1 in 60,000.

Clinical Features

Infants with profound biotinidase deficiency appear normal at birth but signs of the disorder begin to emerge anywhere from a few weeks to several years. Affected children initially show combinations of neurologic and cutaneous symptoms, including seizures, ataxia, hypotonia, developmental delay, hearing loss, decreased vision, rash, conjunctivitis, and fungal infections. Death may even occur due to **severe metabolic decompensation**.

Etiology

Biotinidase deficiency is caused by a genetic deficiency in the biotinidase enzyme, which recycles the common vitamin biotin by cleaving it from lysine residues in certain proteins. Biotinidase deficiency is inherited in an autosomal recessive fashion.

Laboratory Tests

Biotinidase deficiency screening is done by a colorimetric assay. Activity of the enzyme biotinidase, which is reduced in infants with this disorder, is measured. A diminished color in the processed blood specimen indicates that the infant may have biotinidase deficiency.

Laboratory Result Classifications and Corresponding Follow-up Actions for Biotinidase Deficiency

Analyte	Normal Results	Borderline Results	Presumptive Positive
Biotinidase Enzyme (% of normal activity)	>20%	10% - 20%	<10%
	Results are mailed to specimen submitter. No follow-up is required.	NBS waits for the routine second specimen. If not received within 2 to 4 weeks, health care provider is contacted. Results are also mailed to submitter.	If first screen, health care provider is contacted by phone to recommend immediate second specimen. If second screen, immediate diagnostic testing is recommended. Results are mailed to specimen submitter.

Treatment

Treatment for biotinidase deficiency is typically a daily 10 mg oral dose of unbound biotin. Early diagnosis and treatment before the onset of symptoms can avoid all negative consequences of the disorder. Treatment after onset will resolve some symptoms but will not reverse neurological damage.

False Positive/Negative

The enzyme is prone to damage if the sample is delayed in the mail or exposed to high temperatures. This may cause a false positive result.

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Congenital Adrenal Hyperplasia (CAH)

Congenital adrenal hyperplasia (CAH) is characterized by the excessive production of androgenic hormones due to lack of the enzyme 21-hydroxylase. If untreated, CAH can lead to an imbalance in the body's concentration of salts, which in turn can rapidly lead to shock and death. CAH also causes excessive masculinization and extremely premature sexual maturation. Treatment consists of cortisol, which normalizes hormone production. Proper treatment prevents death and stops the masculinization process. Affected females may require surgical correction of masculinized genitalia. The prevalence in the United States is approximately 1 in 16,000. In Washington State, there are, on average, four infants with CAH detected each year.

Clinical Features

Male infants with CAH usually appear normal at birth but develop symptoms within the first week of life. Female infants may show the effects of the virilizing hormones at birth. This usually presents itself as an enlarged clitoris and fusion of the labia majora over the vaginal opening. Occasionally the female infant may be so virilized at birth as to result in erroneous gender assignment. Such newborns should not have a palpable gonad in the labial/scrotal sac. Please alert the newborn screening program immediately if virilizing symptoms are present in an infant so that testing for CAH can be prioritized.

Since infants with CAH may experience a life-threatening salt-wasting crisis within the first week of life, it is critical that the first newborn screening specimen be collected and mailed according to the requirements (prior to discharge and no later than five days of age).

Etiology

CAH is caused by a genetic defect in one of several enzymes involved in converting cholesterol to cortisol. All forms are inherited in an autosomal recessive fashion. The newborn screening test is designed to detect 21-hydroxylase enzyme deficiency, which is responsible for over 90% of all forms of CAH. Therefore, providers should remember that a normal newborn screening result does not rule out other forms of CAH due to other enzyme deficiencies. As with all disorders, providers should proceed with diagnostic testing if clinical symptoms are present despite the results of the newborn screening test.

Laboratory Tests

CAH screening, like thyroid screening, is done by fluoroimmunoassay. The test measures hormone levels of 17-hydroxyprogesterone (17-OHP), which is elevated in infants with the disorder. A 17-OHP level above a certain value will be re-analyzed in duplicate before a classification is made. Due to the variability of the disorder and the age of the infant, the level of 17-OHP may not correlate with the clinical severity of the disease.

Laboratory Result Classifications and Corresponding Follow-up Actions for CAH

Analyte	Normal Results	Borderline Results	Presumptive Positive
17-OHP (ng/ml)	If birth weight is ≥ 2500 g, and age < 6 days, <90; if birth weight is ≥ 2500 g, and age ≥ 6 days, <60; if birth weight is <2500 g, and age < 6 days, <150; if birth weight is <2500g, and age ≥ 6 days, <60;	If birth weight is ≥ 2500 g, and age < 6 days, 90-149; if birth weight is ≥ 2500 g, and age ≥ 6 days, 60-89; if birth weight is <2500 g, and age < 6 days, 150-199; if birth weight is <2500g, and age ≥ 6 days, 60-149;	If birth weight is ≥ 2500 g, and age < 6 days, ≥ 150 ; if birth weight is ≥ 2500 g, and age ≥ 6 days, ≥ 90 ; if birth weight is <2500 g, and age < 6 days, ≥ 200 ; if birth weight is <2500g, and age ≥ 6 days, ≥ 150 ;
	Results are mailed to specimen submitter. No follow-up is required.	Health care provider is contacted by phone to recommend a repeat newborn screening specimen as soon as possible. Results are also mailed to submitter.	Health care provider is contacted by phone to recommend a repeat newborn screening specimen and/or <i>diagnostic testing</i> as soon as possible. Results are also mailed to submitter.

Treatment

Treatment for CAH includes hormone replacement medication. Glucocorticoids (cortisone or hydrocortisone) are given by mouth or injection. Mineralcorticoids are also given if the infant is unable to maintain normal levels of sodium and potassium. Over-medication can cause hypertension in some children; therefore, blood pressure should be monitored. Medications need to be adjusted in the event of vomiting, serious illness, injury, or surgery, and as the infant matures. The Reports & Publications page contains a list of pediatric endocrinologists in Washington and Oregon who should be consulted to help guide diagnosis and treatment.

Females who have virilized genitalia may need surgical correction. The first surgery is usually done before two years of age and is done in stages.

False Positive/Negative

In the first day of life, 17-OHP levels may be transiently elevated. In normal cases this level will resolve after the first 24 hours. In addition, premature or ill infants may exhibit an

elevation in 17-OHP due to physiological stress. It is important that the infant receive follow-up to ensure that the adrenal levels return to the normal range as the infant matures. Steroid medications given to a baby prior to collection of a newborn screen or administered to the mother during pregnancy can cause false-negative results by suppressing the amount of 17-OHP produced by the baby. The screening test is designed to detect the most common cause of CAH, 21 hydroxylase deficiency; it is not effective in detecting other forms.

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Congenital Hypothyroidism (CH)

Congenital hypothyroidism (CH) is characterized by the inability to produce adequate amounts of thyroid hormone, thyroxine (commonly known as T4). Proper production of T4 levels are critical for normal physical growth and mental development. If untreated, CH results in severe neurological and developmental damage. Diagnosis and initiation of appropriate synthetic thyroid hormone replacement (levothyroxine), within the first few weeks of life, followed by regular clinic visits with physicians experienced in the treatment of CH, can prevent growth failure and mental retardation. The prevalence of CH in the United States is approximately 1 in 3,500. In Washington State, there are, on average, 25 to 30 infants with CH detected each year.

Clinical Features

Infants with CH usually appear normal until about three months of age, but it is likely that some brain damage will have already occurred. Clinical symptoms or signs, if present, include prolonged neonatal jaundice, constipation, lethargy, poor muscle tone, feeding problems, a large tongue, mottled and dry skin, distended abdomen, and umbilical hernia. These are not reliable indicators of CH, however, as they are non-specific for CH.

Etiology

The insufficient production of the thyroid hormone T4, which characterizes CH, is most commonly caused by the malformation or malfunction of the thyroid gland. This includes the total or partial failure of the thyroid gland to develop normally (athyreosis or hypoplasia), improper location of the gland (ectopic), or an enzyme deficiency or other chemical disruption in the pathway of thyroid hormone production (dyshormonogenesis).

Laboratory Tests

The newborn screening test for CH measures the infant's TSH (thyroid stimulating hormone) level using a fluoroimmunoassay technique. A TSH above a certain value will be re-analyzed in duplicate before a classification is made. Infants are considered to have a presumptive positive result for CH if the TSH level is between 60-100 mIU/ml depending upon the baby's age when the blood specimen was collected.

Laboratory Result Classifications and Corresponding Follow-up Actions for CH

<i>Analyte</i>	Normal Results	Borderline Results	Presumptive Positive
TSH (micro IU/ml serum)	<55 if ≤ 12 hrs <45 if 13-24 hrs <30 if 25-36 hrs <25 if 37-48 hrs <20 if 49-504 hrs <15 if > 504 hrs	$55-99$ if ≤ 12 hrs $45-99$ if 13-24 hrs $30-59$ if 25-36 hrs $25-59$ if 37-48 hrs $20-59$ if 49-504 hrs $15-59$ if > 504 hrs	≥ 100 if ≤ 24 hrs ≥ 60 if > 24 hrs
	Results are mailed to specimen submitter. No follow-up is required.	NBS waits for the routine second specimen. If not received within 2 to 4 weeks, health care provider is contacted to recommend newborn screening specimen as soon as possible. Results are also mailed to submitter.	Health care provider is immediately contacted by phone to recommend a repeat newborn screening specimen and/or <i>diagnostic testing</i> as soon as possible. Results are also mailed to submitter.

Treatment

Treatment of CH is relatively simple and very effective. Thyroid hormone, in a synthetic pill form (i.e., Synthroid®), is administered orally once daily. The dosage of medication must be adjusted and monitored as the child grows. The Reports & Publications page contains a list of pediatric endocrinologists in Washington and Oregon who can be consulted for confirmation of diagnosis and treatment.

False Positive/Negative

False positives may occur due to early specimen collection. In the first day of life, TSH levels may be transiently elevated. In normal cases this level will resolve after the first 24 hours. It is important that these infants receive follow-up to ensure that the thyroid levels return to the normal range as the infant matures. Other factors that can affect thyroid hormone levels and result in an abnormal screening results are prematurity, maternal medications, such as antithyroid drugs, or topical iodine treatment.

The false-negative rate for CH on the first newborn screening specimen is higher than for all of the other disorders screened. Washington's experience has been that a number of infants with confirmed CH are detected only after their second newborn screen. For maximum

detection of CH, the recommended second newborn screen can be critical for an affected infant.

Special Considerations

Premature infants (birth weight less than 1500 grams) and sick infants have been documented to develop a late onset form of CH. It is therefore recommended that a third newborn screening specimen be collected for these infants between four and six weeks of age. Please see page 19 for more information on the recommended third newborn screen for premature or sick infants.

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Cystic Fibrosis (CF)

Cystic fibrosis (CF) is a treatable disorder that affects salt transport across cells lining the lungs, intestines, liver and reproductive tract. This causes thick, sticky mucus to build up in the lungs and digestive system and other organs of the body. Cystic fibrosis is characterized by chronic pulmonary disease and gastrointestinal abnormalities.

Clinical Features

The first symptom of CF in approximately 15-20% of affected children is meconium ileus, an intestinal obstruction present at birth that usually requires surgery to correct. Other early indicators of CF include recurrent cough, wheezing, repeated or prolonged bouts of pneumonia, chronic abdominal pain, loose stools and failure to thrive.

Etiology

Cystic fibrosis is an autosomal recessive genetic disorder. Affected individuals have mutations in the gene encoding for the cystic fibrosis transmembrane conductance regulator (CFTR). More than 70% of all cases can be traced back to a single common mutation, $\Delta F508$, which is found mainly in Caucasians. CFTR functions as a chloride channel and controls the regulation of other transport pathways. Its malfunction affects the lungs and upper respiratory tract, gastrointestinal tract, pancreas, liver, sweat glands, and genitourinary tract.

Laboratory Tests

The cystic fibrosis screening is performed using a fluoroimmunoassay to measure the level of immunoreactive trypsinogen (IRT) which is elevated in infants with this disorder. An IRT level above a certain cutoff will be reanalyzed in duplicate before a classification is made. No referrals will be made on the basis of a single specimen; elevation on two consecutive newborn screening specimens is the criteria for referral.

Laboratory Result Classifications and Corresponding Follow-up Actions for CF

Analyte	Normal Results	Elevated Results - First Specimen	Elevated Results - Second Specimen
IRT (ng/mL)	<p>If age <6 days, <100.</p> <p>If age ≥6 days, <70.</p>	<p>If age <6 days, >100.</p> <p>If age ≥6 days, >70.</p>	<p>If age ≥6 days, >70.*</p>
	Results are mailed to specimen submitter. No follow-up is required.	DOH waits for the routine second specimen. If not received within 2 to 4 weeks, health care provider is contacted to recommend newborn screening specimen as soon as possible. Results are also mailed to submitter.	<p>If previous screen was elevated, health care provider is contacted by phone to refer for diagnostic testing (sweat test) as soon as possible. If previous screen was normal, mailer note will recommend no further testing unless symptoms present.¹</p> <p>Results are also mailed to submitter.</p>

***Note:** Two specimens with elevated IRT drawn prior to six days of age or within three days of each other do not meet our criteria for persistent elevation. DOH will request a 3rd specimen for newborns when both specimens demonstrating an elevated IRT are drawn prior to six days of age or within three days of each other.

Diagnostic Testing

A positive CF screen should be followed by a diagnostic sweat test. The only acceptable method is the pilocarpine iontophoresis sweat collection followed by quantitative chloride measurement. The sweat test should be performed at a laboratory affiliated with a Cystic Fibrosis Foundation-accredited care center. There are three such centers in Washington State - Children's Hospital and Regional Medical Center in Seattle, Sacred Heart Medical Center in Spokane, and Mary Bridge Children's Health Center in Tacoma (also maintains a laboratory facility in Olympia) - and one center in Portland, Oregon.

¹ A second-tier protocol, implemented in late 2007 to improve sensitivity, calls for a third newborn screening specimen if the IRT on the first screen is greater than 50 ng/mL AND the IRT on the second screen is greater than 85 ng/mL.

Treatment

Treatment for CF depends on both the stage of the disease and the organs involved. Chest physiotherapy should be done daily to help clear thick mucus from the lungs. Patients with CF exhibiting pancreatic insufficiency should take daily vitamin supplements in addition to ingesting pancreatic enzyme supplements with meals to help them absorb enough calories and nutrients to grow and stay healthy. Other types of treatments include antibiotics to fight lung infections and drugs to thin the mucus and improve lung function.

False Positive/Negative

Because Washington State recently began screening for Cystic Fibrosis, information about false positive and false negative rates are not available. We expect that only one out of three babies with positive screening results will be diagnosed with CF.

Special Considerations

While our screening protocol is designed to catch as many newborns with CF as possible, the sensitivity of the CF newborn screen is not 100 percent, so there will be a small number of false negatives (we anticipate about one every two years of screening). Therefore, children exhibiting symptoms, even those whose newborn screening results did not indicate CF, should still be referred for diagnostic testing.

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Galactosemia

Galactosemia is characterized by the inability to metabolize the sugar galactose due to decreased activity of the enzyme galactose-1-phosphate uridylyltransferase (GALT). Galactose is a major constituent of milk sugar, lactose. If untreated, galactosemia results in severe neurological and developmental damage and often neonatal death due to E. coli sepsis. Treatment consists of immediately eliminating dietary intake of lactose by replacing breast or normal formula milk with a lactose-free, soy-based formula. Antibiotics are also prescribed to prevent sepsis. The prevalence of galactosemia in the United States is approximately 1 in 50,000.

Clinical Features

Infants with galactosemia due to profound deficiency of the GALT enzyme usually appear normal at birth, but soon develop signs of the disorder after they begin feeding on milk. Symptoms may include a failure to thrive and vomiting or diarrhea after ingesting milk. Hepatomegaly and jaundice are common by the end of the first week of life. Infants who survive untreated may develop liver disease, kidney damage, cataracts, growth failure, mental retardation, and ovarian failure in girls. Many of the problems associated with galactosemia can be prevented if the baby is diagnosed and treated early by switching to a soy-based formula and eliminating galactose and lactose intake for life. Infants with partial deficiency of the GALT enzyme typically experience few, if any, symptoms, even with continued exposure.

Etiology

Galactosemia is caused by a genetic deficiency in the enzyme galactose-1-phosphate uridyltransferase (GALT), which helps metabolize the sugar galactose. It is inherited in an autosomal recessive fashion.

Laboratory Tests

Galactosemia screening is done by a fluorometric assay that measures activity of the GALT enzyme. Diminished fluorescence in the processed blood specimen indicates that the infant may have galactosemia. A second-tier test will be performed on screen positive specimens if needed to further clarify the significance of the initial test results.

Laboratory Result Classifications and Corresponding Follow-up Actions for Galactosemia

<i>Analyte</i>	Normal Results	Borderline Results	Presumptive Positive
GALT (Units/g Hb)	>2.5	2.0-2.5	< 2.0
	Results are mailed to specimen submitter. No follow-up is required.	If first screen, health care provider is contacted by phone to request routine second specimen. If two abnormal screens, diagnostic testing is recommended. Results are mailed to specimen submitter.	Health care provider is immediately contacted by phone to recommend substitution of soy formula for breast milk or commercial based formula and prompt diagnostic testing. Results are mailed to specimen submitter.

Treatment

The main treatment for galactosemia is elimination of galactose and lactose from the diet. Dietary management needs to begin as soon as possible and continue throughout life. Once diagnosed, the infant should be changed to a soy-based formula that does not contain galactose. Antibiotics are normally prescribed to prevent sepsis, even after a child has been switched to a soy-based formula, as sepsis can still arise if the child has previously ingested galactose.

False Positive/Negative

The enzyme evaluated in screening is prone to damage if the sample is delayed in the mail or exposed to high temperatures. This may cause a false positive result.

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Sickle Cell Disease and Other Hemoglobinopathies

Hemoglobinopathies are inherited abnormalities in the structure or amount of hemoglobin. Infants with normal hemoglobin will have a screening result of FA, indicating that both fetal and adult hemoglobin is present. In sickle cell disease the predominant hemoglobin is hemoglobin S (HbS). When oxygenated, HbS functions normally. When under reduced oxygen, it forms crystal-like rods, distorting the red blood cells into a sickle shape. These red blood cells are easily destroyed and tend to stick together, blocking blood vessels. This causes many of the painful symptoms and organ damage associated with sickle cell disease. The frequency of hemoglobinopathies varies among ethnic groups. Sickle hemoglobin is found most commonly among people with African, Mediterranean, Middle Eastern, and Indian ancestry. In the United States, sickle cell disease is found in virtually all ethnic groups with a prevalence of approximately 1 in 10,000 in the general population. However, it is present in approximately 1 in 400 persons of African ancestry. In Washington State, there are, on average, seven infants with sickle cell disease detected each year. In addition, another ten infants are found through newborn hemoglobin screening to have other clinically significant hemoglobinopathies such as transfusion dependent thalassemias.

Clinical Features

With the exception of alpha thalassemia major (Fetal Hydrops Syndrome), infants affected with hemoglobinopathies appear normal at birth. With sickle cell disease, anemia develops in the first few months of life as the amount of fetal hemoglobin decreases and HbS increases. Enlargement of the spleen results from the trapping of sickled red blood cells in the spleen (splenic sequestration). If acute, this can rapidly cause severe anemia and transfusions may be necessary. Splenic sequestration can result in death.

Infants and children with sickle cell disease are particularly susceptible to bacterial infections. This may manifest as pneumonia, meningitis, osteomyelitis, or septicemia. Prompt antibiotic treatment can be lifesaving. Studies have also shown that prophylactic oral penicillin and folic acid started early and maintained through age six, decreases the number of episodes of infections and death.

Health problems due to sickle cell disease are highly variable. Pain is the most common symptom of sickle cell disease. Pain episodes can occur at any time and in any part of the body. However, they occur most often in the arms, legs, chest and abdomen. These episodes vary in frequency, severity, and length. Some individuals rarely have painful episodes; others have them frequently. When they occur, they can last from a few hours to several days and can be severe enough to require hospitalization and the use of very strong pain medication.

Anemia (a low number of red blood cells) is the another common medical problem of sickle cell disease. This occurs because sickled red blood cells don't live as long as normal red blood cells and a person with sickle cell disease cannot make red blood cells fast enough to keep up with the rapid breakdown.

In the adolescent and adult with sickle cell disease, other complications can occur due to the problems with impaired circulation, the premature breakdown of the red blood cells, and damage to the spleen and other body organs. These include jaundice, slower growth and onset of puberty, fatigue, gallstones, shortness of breath, blood in the urine, and

stroke. There is currently no cure for sickle cell disease, but with appropriate medical care and management, the complications of sickle cell disease can be minimized. The other significant hemoglobinopathies reported by the Newborn Screening Program include hemoglobin C, D, E, and alpha thalassemias which have variable clinical manifestations ranging from mild to severe anemia. All have reproductive implications for families.

Etiology

Sickle cell disease is a recessively inherited defect of the beta globin chains. A single nucleotide change in the beta globin gene results in the production of S hemoglobin. Sickle cell disease results if both beta globin genes carry the S mutation or if one gene has the S mutation and the other produces abnormal hemoglobin such as C, D or beta thalassemia.

Other Clinically Significant Hemoglobinopathies

Other clinically significant hemoglobinopathies may result from a structural change in the alpha or beta globin chain or a change in their rate of production. Thalassemias are caused by decreased synthesis of normal globin chains and therefore decreased production of hemoglobin A.

Carrier Detection (Hemoglobin Traits)

The identification of infants who are carriers of hemoglobin traits (i.e.: those who have genes that produce both normal and abnormal hemoglobin) is a by-product of the screening for sickle cell disease and other hemoglobinopathies. The Newborn Screening Program reports all traits detected, including hemoglobin S, C, D, E, Bart's and unidentified variants. Most hemoglobin traits are not associated with clinical symptoms or the need for treatment. However, because they have reproductive implications for the parents and the child, the health care provider is notified by mail of trait status and provided with information to share with the family. It is suggested that the parents of a child with a hemoglobin trait should be offered genetic counseling and testing to determine if future children are at risk for disease.

Laboratory Tests

Initial hemoglobin screening is performed by isoelectric focusing (IEF), in which hemoglobin bands are identified by their migration distance in an electric field. Abnormal findings on IEF are confirmed by High Performance Liquid Chromatography (HPLC). A second-tier test will be performed on screen positive specimens if needed to further clarify the significance of the initial test results.

Hemoglobins are by far the most complex of the conditions detected by Newborn Screening. More than a dozen genes are involved in hemoglobin production and over 800 abnormalities have been described by researchers and clinicians. Also, a variety of combinations are possible for any individual. Listed in the table below are some of the more commonly seen newborn hemoglobin screening findings:

Laboratory Result Classifications and Corresponding Follow-up Actions for Abnormal Hemoglobins

Hemoglobin Phenotype	Likely Genotype	NBS Follow-up Action
FA	Normal	None
AF or AA	Transfusion or older infant	If transfused, report by letter and recommend rescreening 120 days after last transfusion.
FSS	Sickle cell disease	Contact health care provider (HCP) by phone and recommend immediate referral to a pediatric hematologist.
FS- or FSA	Sickle beta thalassemia	
FSC	Sickle C disease	
FSD	Sickle D disease	
F only	Beta thalassemia major	Contact HCP by phone and recommend immediate referral to a pediatric hematologist.
FE-	Hemoglobin E beta thalassemia	Report by letter recommending a diagnostic work-up.
FEE	Hemoglobin E disease	
FA + high Bart's	Hemoglobin H disease	
FCC	Hemoglobin C disease	
FAS	Hemoglobin S trait	Report by letter to HCP suggesting family studies and genetic counseling.
FAE	Hemoglobin E trait	
FAC	Hemoglobin C trait	
FAD	Hemoglobin D trait	
FA+Bart's	Bart's hemoglobin, marker for alpha thalassemia	Report by letter to HCP recommending follow-up testing to determine clinical significance for child and reproductive implications for family.
FA + Variant	Unidentified variant hemoglobin trait	Report by letter to HCP recommending follow-up only if accompanied by clinical signs or <i>family history</i> of hemoglobinopathy.

Treatment

Infants with sickle cell disease should take prophylactic penicillin until the age of six. Parents need education on how to take and respond to a temperature, care for acute illness, and how to assess spleen size. It is also important that affected children receive all recommended vaccinations including the pneumococcal vaccine. Consultation with a pediatric hematologist is strongly advised. In addition, continued family education, support groups, and genetic counseling are an important part of treatment for the child and family.

False Positive/Negative

A false positive hemoglobin result may occur when beta thalassemia occurs in combination with a structural change in the beta globin chain. For example, a child with hemoglobin S trait may appear to have sickle beta thalassemia due to the biological variation in the switch from fetal to adult hemoglobin. The Newborn Screening Program will provide appropriate recommendations for the follow up of such infants. False negative results can result from degradation due to specimen age or unusual storage conditions. Most affected are unstable hemoglobins such as Bart's.

Special Considerations

The newborn screening specimen should be obtained prior to transfusing a newborn. After transfusion the hemoglobin results are masked by the donor's blood and hemoglobin testing is invalid. If the newborn screening specimen is not obtained prior to the transfusion, an additional specimen should be collected 120 days after the last transfusion. However, this should not delay collection of the first and second specimens at the normal recommended times. It is still possible to screen for the other disorders despite the transfusion.

A newborn screening specimen should always be mailed within the 24 hours after it is collected. Specimens received fourteen days after collection cannot be screened for hemoglobinopathies due to the degradation of the red blood cells. A repeat specimen will be required.

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Newborn Hearing Screening

Hearing loss affects approximately three newborns per one thousand but can often be detected at birth by a simple, inexpensive test performed before hospital discharge. This early detection allows for timely diagnosis and intervention.

Newborn hearing screening is not mandated in Washington State but is currently done in all birthing hospitals. In 2006, over 95% of hospital-born infants were screened for hearing loss in Washington.

The Department of Health established the Early Hearing Loss, Detection, Diagnosis, and Intervention (EHDDI) program to help coordinate a statewide effort to improve and support screening, diagnostic, and early-intervention services for infants born with hearing loss, or increased risk for late onset hearing loss in childhood.

The primary goals of the EHDDI program are to ensure that all infants born in the state of Washington:

- Are screened for hearing loss before hospital discharge or by *one* month of age
- Receive diagnostic audiological evaluation by *three* months of age
- Are enrolled in early intervention services by *six* months of age if needed

To achieve these goals, the EHDDI program developed a tracking and surveillance system, which follows infants from hearing screening through diagnostic evaluation. Hearing screening results are reported to the EHDDI program by hospitals and clinics using a revised Newborn Screening collection card. These cards are processed in collaboration with the Newborn Screening Program at the State Public Health Laboratory.

If you would like more information about EHDDI, please contact the Washington State Department of Health EHDDI Program, at (206) 418-5609 or ehddi2@doh.wa.gov. Or visit them on the web at: <http://www.doh.wa.gov/cfh/mch/genetics/ehddi>.

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